In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 02-1237V
Filed: September 26, 2015
For Publication

COLLEEN BOSTON MADARIAGA and JAMES ALLEN, parents and guardians of A.A., a minor,	*	Measles, Mumps, and Rubella ["MMR"] Vaccine; Autism; Mitochondrial Disorder; Diagnosis; Metabolic Stress; Regression; Treating Physicians; Expert Qualifications
Petitioners,	*	
v.	*	
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Sylvia Chin-Caplan, Conway, Homer & Chin-Caplan, Boston, MA, for petitioners.
Heather Pearlman, U.S. Dept. of Justice, Washington, D.C., for respondent.

DECISION[1]

Vowell, Special Master:

On September 23, 2002, Colleen Allen ["petitioner"] filed a short-form "Petition for Vaccine Compensation" for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. §300aa-10, *et seq.*[2] ["Vaccine Act" or "Program"] on behalf of her daughter, A.A. An amended petition, which now constitutes the operative petition for this claim, was filed on March 1, 2012.[3] On May 9, 2012, petitioner moved

[1] The E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002) requires that this decision be publically available. In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will redact such material from public access.

[2] The National Vaccine Injury Compensation Program ["Vaccine Program"] is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. § 300aa-10 *et seq.* (2012). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

[3] Hereinafter, unless the context clearly indicates otherwise, any reference to "petition" is to this Amended Petition.

to amend the case caption to reflect her name change following remarriage, and to add James Allen, A.A.'s father, as a petitioner.

In summary, petitioners claim that the measles, mumps, and rubella ["MMR"] vaccine A.A. received on October 23, 2000, caused her to suffer from "mitochondrial pervasive developmental disorder"[4]—a "particular form of autistic spectrum disorder caused by an inborn error of mitochondrial metabolism." Petition ¶¶ Introduction, 15. According to their experts, A.A. had an underlying mitochondrial disorder—present since birth—that made her vulnerable to the inflammatory effects of the MMR vaccine. The vaccine, which constituted an immunological stressor, overwhelmed A.A.'s already impaired mitochondrial function and caused extensive cell death in her brain. As a result of this damage, she experienced an acute regression and ultimately developed mitochondrial autism. *See* Petitioners' Post-Hearing Brief, filed Nov. 27, 2013, at 30-60.

For the reasons set forth below, I find that the record does not contain preponderant evidence establishing entitlement to compensation.

I. Procedural History.

A. The Omnibus Autism Program ["OAP"].

Beginning in 1997, but peaking numerically in 2002-03, thousands of petitions were filed alleging either that the measles, mumps, and rubella ["MMR"] vaccine or thimerosal, an ethyl mercury preservative used in multi-dose vials of vaccine, caused ASD. The sheer volume of petitions filed—more than 1,300 new petitions in 2002 alone—led to the creation of the OAP.[5] Omnibus programs had been used previously to make causation determinations in groups of cases alleging that a particular vaccine caused a specific injury, but the OAP was, by far, the largest such grouping of similar cases.[6] By filing their original short-form petition, an abbreviated petition authorized by Autism General Order #1, petitioners opted into the OAP.

Following a series of meetings with an informal advisory committee comprised of petitioners' counsel representing many of the Program claimants plus legal and medical representatives of the Secretary of Health and Human Services, the Office of Special Masters adopted a plan that would allow a period of discovery, followed by the selection and litigation of test cases on the theories of causation presented. Autism General

[4] Synonymous with "mitochondrial pervasive development disorder" are the terms "autism secondary to mitochondrial disease" and "mitochondrial autism." Tr. at 236-37.

[5] *See* Autism General Order #1, issued July 3, 2002 (found at 2002 WL 31696785, 2002 U.S. Claims LEXIS 365, or http://www.uscfc.uscourts.gov/sites/default/files/autism/Autism+General+Order1.pdf) (last visited on Sept. 8, 2015).

[6] *See Hennessey v. Sec'y, HHS,* No. 01-190V, 2009 WL 1709053 (Fed. Cl. Spec. Mstr. May 29, 2009), *aff'd,* 91 Fed. Cl. 126 (2010) (discussing the different types of omnibus proceedings conducted in the Vaccine Program).

Order #1 at 2-3. The conclusions reached on general causation in the test cases would be used to resolve the remaining individual claims. *Id.* at 3. Petitioners were allowed to "opt in" or "opt out" of the proceedings and future claimants could automatically "opt in" by filing the short form petition included as Attachment B to Autism General Order #1. Autism General Order #1 at 6-8.

Attorneys representing petitioners created the Petitioners' Steering Committee ["PSC"] to coordinate the OAP litigative effort. The PSC acknowledged that there was insufficient evidence at the time the OAP was created to prove vaccine causation, but averred that such evidence could be found through discovery and ongoing scientific investigations. Petitioners sought and received an extended period of time to conduct discovery and prepare to litigate test cases.

Nearly five years after the OAP was created, litigation in the test cases began. The PSC presented two different theories on the causation of ASD in two sets of test cases. The first alleged that thimerosal-containing vaccines and the MMR vaccine, in combination, could cause ASD (Theory 1). The second alleged that thimerosal-containing vaccines could cause ASD (Theory 2).[7]

Decisions in each of the three Theory 1 test cases, which were tried in 2007, rejected petitioners' causation theories. *Cedillo v. Sec'y, HHS,* No. 98-916V, 2009 WL 331968 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff'd*, 89 Fed. Cl. 158 (2009), *aff'd*, 617 F.3d 1328 (Fed. Cir. 2010); *Hazlehurst v. Sec'y, HHS,* No. 03-654V, 2009 WL 332306 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff'd*, 88 Fed. Cl. 473 (2009), *aff'd*, 604 F.3d 1343 (Fed. Cir. 2010); *Snyder v. Sec'y, HHS,* No. 01-162V, 2009 WL 332044 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff'd*, 88 Fed. Cl. 706 (2009).[8]

Decisions in the three Theory 2 test cases, which were tried in 2008, also rejected the causation theory presented. Petitioners did not seek review of the special masters' decisions. *Dwyer,* 2010 WL 892250; *King v. Sec'y, HHS,* No. 03-584V, 2010 WL 892296 (Fed. Cl. Spec. Mstr. Mar. 12, 2010); *Mead*, 2010 WL 892248.

An impressive body of medical and scientific evidence was adduced in the OAP test cases, with the three special masters who heard this evidence finding that the issue of vaccine causation was "*not a close case.*" *See, e.g.*, *King*, 2010 WL 892296, at *90 (emphasis in original); *Snyder*, 2009 WL 332044, at *198. Each of the three special

[7] A detailed discussion of the OAP can be found at *Dwyer v. Sec'y, HHS,* No. 03-1202V, 2010 WL 892250, at *2 (Fed. Cl. Spec. Mstr. Mar. 12, 2010). In keeping with the intent that the OAP test case evidence be available to aid in resolving the remaining OAP cases, the evidence (including expert reports, transcripts of testimony, trial presentation materials (trial exhibits), and lists of the medical journals and other documents filed by the parties) is posted on the Court of Federal Claims website (http://www.uscfc.uscourts.gov/docket-omnibus-autism-proceeding) (last visited on May 11, 2015). The parties in the test case hearings all filed explicit written consent to make these materials publicly available. *See, e.g.*, *Mead v. Sec'y, HHS,* No. 03-215V, 2010 WL 892248 (Fed. Cl. Spec. Mstr. Mar. 12, 2010), at *1 n.1 (referencing petitioners' and respondent's written consent in that case).

[8] Petitioners did not appeal the Court of Federal Claims decision in *Snyder* to the Federal Circuit.

masters independently determined that the medical theories advanced were not reliable and that the test case petitioners had failed to produce preponderant evidence of causation. The OAP test case litigation concluded in 2010, with the last Federal Circuit decision affirming the dismissal of the final Theory 1 test case.[9]

During the period between the test case hearings and the final appellate action on the test case decisions, petitioners in this case, like others in the OAP, were ordered to file the medical records necessary to establish that the petition was timely filed. *See* Order, issued Mar. 13, 2009, at 5. Petitioners filed the required medical records on June 11, 2009 and July 22, 2009. *See* Petitioners' Exhibits ["Pet. Exs."] 1-10. On August 14, 2009, respondent filed a statement indicating that the claim was timely filed and involved a diagnosis of ASD. Because the claim was determined to have been timely filed, petitioners were ordered to file all remaining medical records. *See* Order, issued Aug. 24, 2009, at 1-2. Petitioners filed the required medical records on November 19, 2009 and December 23, 2009. *See* Pet. Exs. 11-14.

With appellate review completed, orders were issued on a rolling basis to the remaining 4,800 petitioners, requiring them to inform the court whether they intended to dismiss their case or proceed on a different theory or with different evidence. Petitioners were ordered to inform the court if they wished to proceed with their claim. *See* Order, issued May 12, 2011, at 3. If petitioners wished to continue with their claim, they were ordered to file an amended petition, setting forth their theory of causation.[10] *Id.* During the next ten months, petitioners filed additional medical records. *See* Pet. Exs. 15-20. On March 1, 2012, they filed their amended petition.

B. Procedural History Post-OAP.

On March 15, 2012, I held a telephonic status conference to discuss petitioners' amended petition and next steps in this case. I ordered petitioners to file any outstanding medical records and a supplemental statement of completion by March 30, 2012, and expert reports by May 14, 2012. *See* Scheduling Order, issued Mar. 15, 2012.

On March 30, 2012, petitioners filed a supplemental statement of completion indicating that they had filed all of the medical records to substantiate the amended petition.

After requesting and receiving additional time to file their expert reports (s*ee* Motions, filed May 14, 2012; July 16, 2012), petitioners filed an expert report, curriculum vitae ["CV"], and two supporting documents from Dr. Richard Kelley; and an expert report, CV, and one article from Dr. Andrew Zimmerman on July 19, 2012. *See* Pet.

[9] *Cedillo v. Sec'y, HHS*, 617 F.3d 1328 (Fed. Cir. 2010).

[10] Petitioners were cautioned that the special masters did not intend to re-litigate the test case theories, and that a reasonable basis to proceed would require either new evidence on the old theories or new theories of causation. *See* Order, issued May 12, 2011, at 2.

Exs. 23-26.[11] Although both experts treated A.A., they did so long after onset of her ASD symptoms.

On November 16, 2012, respondent filed her supplemental Rule 4(c) report; an expert report, CV, and eight articles from Dr. Stephen Cederbaum; and an expert report, CV, and seven articles from Dr. Max Wiznitzer, after seeking one extension of time. *See* Respondent's Rule 4(c) report; Respondent's Exhibits ["Res. Exs."] A-S.

On January 9, 2013, I held a telephonic status conference pursuant to Vaccine Rule 5[12] to discuss the expert reports and positions of the parties. During the status conference, the parties agreed that the case was ready for a hearing to address the experts' disagreement with regard to causation. I noted that certain factual disputes still existed and that I would need the experts to testify on these issues as well. I ordered the parties to file a joint status report by January 24, 2013, providing possible hearing dates. *See* Scheduling Order, issued Jan. 9, 2013.

After the parties filed their joint status report, I scheduled a four-day entitlement hearing in Washington, D.C. from July 9-12, 2013. *See* Pre-Hearing Order, issued Jan. 28, 2013. On April 5, 2013, I ordered the parties to file any outstanding evidence on which they intended to rely by May 24, 2013. *See* Pre-Hearing Order, issued Apr. 5, 2013, at 1. I also ordered the parties to file (1) a joint submission identifying any disputed and non-disputed issues; (2) a memorandum containing their basic factual contentions and applicable legal authority; (3) an affidavit from each fact witness, if not previously filed; and (4) witness lists. *Id.* at 2.

Over the next several months, petitioners timely filed additional medical literature,[13] updated school and medical records, and relevant video evidence. Respondent also filed additional medical literature.[14] On June 10, 2013, the parties filed their pre-hearing submissions. Petitioners indicated that they would be calling four witnesses, including two expert witnesses, to testify at the hearing. *See* Pet. Pre-Hearing Submission, filed June 10, 2013, at 34. Respondent indicated that she would be calling both of her expert witnesses to testify. *See* Res. Pre-Hearing Submission, filed June 10, 2013 (ECF No. 80), at 16. Petitioners also filed the affidavits of James Allen (A.A.'s father) and Susan Edick (A.A.'s aunt), A.A.'s vaccination record, and additional video and photographic evidence.

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[11] The supporting documents from Dr. Kelley included A.A.'s amino acid profile (Pet. Ex. 23A) and an unpublished protocol titled "Evaluation and Treatment of Patients with Autism and Mitochondrial Disease (Pet. Ex. 23B). Doctor Zimmerman submitted J. Poling, et al., *Developmental Regression and Mitochondrial Dysfunction In a Child with Autism*, J. CHILD NEUROL., 21 (2): 170-72 (2006), filed as Pet. Ex. 25, Tab A [hereinafter "Poling, Pet. Ex. 25A"].

[12] RCFC, Appendix B.

[13] *See* Pet. Exs. 27-59, 65-74.

[14] *See* Res. Exs. T-CC.

Finally, the parties filed a joint submission identifying the disputed and non-disputed issues. *See* Joint Pre-Hearing Submission, filed June 10, 2013 (ECF No. 79). Specifically, the parties disputed (1) "the state of A.A.'s health and development prior to October 23, 2000"; (2) whether "A.A. suffer[ed] a developmental regression after her receipt of the October 23, 2000, MMR vaccination[,]" and, if so, when the regression occurred; (3) whether the "October 23, 2000, MMR vaccinations cause[d]-in-fact any of A.A.'s subsequently diagnosed developmental, neurological, or mitochondrial issues"; and (4) whether "A.A. has a mitochondrial disease[.]" *Id.* at 1-2.

On June 20, 2013, petitioners filed additional video evidence. *See* Pet. Ex. 80. On June 28, 2013, I held a telephonic status conference with the parties to discuss the pending hearing. I also discussed the video evidence filed by petitioners. Petitioners' counsel confirmed that the video was a compilation of clips taken from a more complete recording. I explained that although the edited clips could be used during testimony, the entire recording should be filed into the record for review. I also requested that any additional videos of A.A. from the first two years of her life be filed, if available. *See* Scheduling Order, issued July 1, 2013.

In compliance with my order, petitioners filed an unedited version of the video. *See* Pet. Ex. 81. Petitioners also filed a status report stating that "after a diligent search, . . . they were unable to locate any additional videos of A.A. from one to two years of age." *See* Status Report, filed July 2, 2013, at 2.

The entitlement hearing was held as scheduled, from July 9-12, 2013. Four physicians testified at the four day hearing. Mr. Allen and Ms. Edick also testified in person. A.A. also attended part of the hearing, and I had the opportunity to meet and speak with her. Following the hearing, I set a schedule for the identification and correction of transcript errors and the submission of post-hearing briefs. *See* Post-Hearing Order, issued on July 30, 2013.

On August 1, 2013, petitioners filed several exhibits used during the hearing. *See* Trial Exhibits ["Trial Exs."] 1-5. On September 3, 2013, I filed Court Exhibit I, a medical journal article, and provided the parties and their experts an opportunity to comment on the exhibit. *See* Res. Resp. to Court's Sept. 3, 2013 Order and Ex., filed Sept. 30, 2013; Res. Ex. DD; Pet. Resp. to Court's Sept. 3, 2013 Order and Ex., filed Oct. 3, 2013; Pet. Ex. 82.

On September 6, 2013, the parties submitted their joint corrections to the transcript. A corrected version of the transcript was filed on September 19, 2013.[15]

Simultaneous post-hearing briefs were filed on November 27, 2013. On December 12, 2013, the parties submitted responses to the post-hearing briefs, completing the record.

[15] All references to the transcript are to the corrected version.

II. Legal Standards Applying to Off-Table Causation Claims.

When petitioners allege an off-Table injury, eligibility for compensation is established when, by a preponderance of the evidence, petitioners demonstrate that the vaccinee received, in the United States, a vaccine appearing on the Table and sustained an illness, disability, injury, or condition caused by the vaccine or experienced a significant aggravation of a preexisting condition. They must also demonstrate that the condition has persisted for more than six months.[16] Vaccine Act litigation rarely concerns whether the vaccine appears on the Table, the geographical location of administration, or whether the symptoms have persisted for the requisite time. Rather, in the very small minority of Vaccine Act cases that proceed to a hearing, the most common issue to be resolved by the special master is whether the injury alleged was caused by the vaccine.

To establish legal causation in an off-Table case, Vaccine Act petitioners must establish by preponderant evidence: (1) a reliable medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a proximate temporal relationship between vaccination and injury. *Althen v. Sec'y, HHS*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *see de Bazan v. Sec'y, HHS*, 539 F.3d 1347, 1351-52 (Fed. Cir. 2008); *Caves v. Sec'y, HHS*, 100 Fed. Cl. 119, 132 (2011), *aff'd per curiam*, 463 Fed. Appx. 932 (Fed. Cir. 2012) (specifying that each *Althen* factor must be established by preponderant evidence). The applicable level of proof is the "traditional tort standard of 'preponderant evidence.'" *Moberly v. Sec'y, HHS*, 592 F.3d 1315, 1322 (Fed. Cir. 2010) (citing *de Bazan,* 539 F.3d at 1351); *Pafford v. Sec'y, HHS*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Capizzano v. Sec'y, HHS*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *Althen*, 418 F.3d at 1278). Although special masters are not bound by the formal rules of evidence generally applicable in federal courts, they are required to find evidence reliable before they may consider it. *Knudsen v. Sec'y*, *HHS,* 35 F.3d 543, 548-49 (Fed. Cir. 1994) (Petitioner has the burden to present a reliable and reputable medical theory, which must be "legally probable, not medically or scientifically certain."); *Daubert v. Merrell Dow Pharmaceuticals,* 509 U.S. 579, 590 (1993) (holding that scientific evidence and expert opinions must be reliable to be admissible). The preponderance standard "requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence." *In re Winship*, 397 U.S. 358, 371 (1970) (Harlan, J., concurring) (internal quotation and citation omitted).

Another formulation of the causation requirement in off-Table cases is the "Can it cause?" and "Did it cause?" inquiries used in toxic tort litigation. These queries are also referred to as issues of general and specific causation. Prong 1 of *Althen* has been characterized as an alternative formulation of the "Can it cause?" or general causation query. Prong 2 of *Althen*, the requirement for a logical sequence of cause and effect

[16] Section 13(a)(1)(A). This section provides that petitioner must demonstrate "by a preponderance of the evidence the matters required in the petition by section 300aa–11(c)(1) . . . ." Section 11(c)(1) contains the factors listed above, along with others not relevant to this case.

between the vaccine and the injury, has been characterized as addressing the "Did it cause?" or specific causation query. *See Pafford v. Sec'y, HHS*, No. 01-165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (2006). Prong 3 of *Althen*, the requirement that the injury sustained occur within a medically appropriate interval after vaccination, is subsumed into the other inquiries. Even if a particular vaccine has been causally associated with an injury, petitioner must still establish facts and circumstances that make it more likely than not that this vaccine caused the particular injury. Timing may be one of those circumstances.

Whether a case is analyzed under *Althen* or the "Can it cause?" formulation, petitioners are not required to establish identification and proof of specific biological mechanisms, as "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280. Petitioners need not show that the vaccination was the sole cause, or even the predominant cause, of the injury or condition; showing that the vaccination was a "substantial factor"[17] in causing the condition, and was a "but for" cause, are sufficient for recovery. *Shyface v. Sec'y, HHS*, 165 F.3d 1344, 1352 (Fed. Cir. 1999); *see also Pafford,* 451 F.3d at 1355 (petitioners must establish that a vaccination was a substantial factor and that harm would not have occurred in the absence of vaccination). Petitioners cannot be *required* to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect," *Capizzano*, 440 F.3d at 1325, but the special master may certainly consider such evidence when filed. *Andreu v. Sec'y, HHS,* 569 F.3d 1367, 1379 (Fed. Cir. 2009) (Special masters may consider medical literature and epidemiological evidence, when it is submitted, in "reaching an informed judgment as to whether a particular vaccine likely caused a particular injury."). Causation is determined on a case by case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen,* 35 F.3d at 548 (Fed. Cir. 1994). Close calls regarding causation must be resolved in favor of petitioners. *Althen*, 418 F.3d at 1280; *but see Knudsen*, 35 F.3d at 550 (when evidence is in equipoise, the party with the burden of proof fails to meet that burden).

In Vaccine Act cases, special masters are frequently confronted by expert witnesses with diametrically opposing positions on causation. When experts disagree, many factors influence a factfinder to accept some testimony and reject other contrary testimony. As the Federal Circuit noted, "[a]ssessments as to the reliability of expert testimony often turn on credibility determinations, particularly in cases . . . where there is little supporting evidence for the expert's opinion." *Moberly*, 592 F.3d at 1325-26.

[17] The Restatement (Third) of Torts has eliminated "substantial factor" in the factual cause analysis. § 26 cmt. j (2010). Because the Federal Circuit has held that the causation analysis in the Restatement (Second) of Torts applies to off-Table Vaccine Act cases (*see Walther v. Sec'y, HHS*, 485 F.3d 1146, 1151 (Fed. Cir. 2007); *Shyface*, 165 F.3d at 1352), this change does not affect the determination of legal cause in Vaccine Act cases: whether the vaccination is a "substantial factor" is still a consideration in determining whether it is the legal cause of an injury.

Objective factors, including the qualifications, training, and experience of the expert witnesses; the extent to which their proffered opinions are supported by reliable medical research and other testimony; and the factual basis for their opinions are all significant factors in determining what testimony to credit and what to reject. *Lalonde v. Sec'y, HHS,* 746 F.3d 1334, 1340 (Fed. Cir. 2014) (noting that "as the finder of fact, the special master was responsible for assessing the reliability of [the expert's] testimony by looking for reliable medical or scientific support" (citing *Moberly*, 592 F.3d at 1324-25)).

Congress contemplated that special masters would weigh and evaluate opposing expert opinions in determining whether petitioners have met their burden of proof. Congress clearly specified petitioners' burden of proof in off-Table cases as the preponderance of the evidence standard. It directed special masters to consider the evidence as a whole, but stated that special masters are not bound by any particular piece of evidence contained in the record.[18] In weighing and evaluating expert opinions in Vaccine Act cases, the same factors the Supreme Court has considered important in determining their admissibility provide the weights and counterweights. *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 149-50 (1999); *Terran v. Sec'y, HHS*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). As the Supreme Court has noted, a trial court is not required to accept the *ipse dixit* of any expert's medical or scientific opinion because the "court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

Although the Federal Rules of Evidence and cases interpreting them are not binding on special masters, they can guide their decisions. *Daubert*, which interpreted Rule 702 of the Federal Rules of Evidence, provides a useful framework for evaluating scientific evidence in Program cases. *Terran*, 195 F.3d at 1316 (concluding that it was reasonable for the special master to use *Daubert* to evaluate the reliability of an expert's testimony); *Cedillo*, 617 F.3d at 1339 (noting that special masters are to consider all relevant and reliable evidence filed in a case and may use *Daubert* factors in their evaluation of expert testimony); *Davis v. Sec'y, HHS*, 94 Fed. Cl. 53, 67 (2010) (describing the *Daubert* factors as an "acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted . . . by special masters in vaccine cases"); *see also Snyder*, 88 Fed. Cl. 706, 718 (2009) (quoting *Ryman v. Sec'y, HHS*, 65 Fed. Cl. 35, 40-41 (2005) (special masters perform gatekeeping function when determining "whether a particular petitioner's expert medical testimony supporting biological probability may be admitted or credited or otherwise relied upon" and as a "trier-of-fact [a special master] may properly consider the credibility and applicability of medical theories")). The special master's use of the *Daubert* factors to evaluate the reliability of expert opinions in Vaccine Act cases has been cited with approval by the Federal Circuit more recently in *Andreu,* 569 F.3d at 1379 and *Moberly,* 592 F.3d at 1324. *See also Vaughan v. Sec'y, HHS,* 107 Fed. Cl. 212, 222 (2012) ("The Federal

[18] *See* § 13(a)(1)(A) (preponderance standard); § 13(a)(1) ("Compensation shall be awarded . . . if the special master or court finds on the record as a whole . . . ."); § 13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation and special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record).

Circuit has repeatedly stated that the Special Master may refer to *Daubert* to assess reliability of expert testimony in vaccine cases."). Special masters decide questions of credibility, plausibility, probability, and reliability, and ultimately determine to which side the balance of the evidence is tipped. *See Pafford*, 451 F.3d at 1359.

Bearing all these legal standards in mind, I now turn to the evidence presented in this case.

III. Summary of Relevant Medical Records.

A. Early Medical and Developmental History.

A.A., petitioners' first child, was born in mid-July, 1999. She was a healthy newborn, with Apgar scores of 8 and 9.[19] Pet. Ex. 1, p. 19. Her newborn exam was normal.[20] Pet. Ex. 3, pp. 5, 16.

During her first year of life, A.A. received routine childhood immunizations[21] and was generally healthy with no major illnesses. Her medical records from Countryside Pediatrics ["Countryside"], her primary care provider,[22] reflect scheduled well child examinations, as well as periodic unscheduled visits due to minor illnesses.

A.A. was seen for her two-month well child visit on September 17, 1999, and was noted to be "doing very well." Pet. Ex. 9, p. 13. The medical report indicated a normal physical examination, and normal development as measured by six defined skills, including whether she regarded a face directly and responded to sound.[23]

[19] The Apgar score is a numerical assessment of a newborn's condition (with lower numbers indicating problems), usually taken at one minute and five minutes after birth. The score is derived from the infant's heart rate, respiration, muscle tone, reflex irritability, and color, with from zero to two points awarded in each of the five categories. *See* DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (32d ed. 2012) ["DORLAND'S"] at 1682; NELSON TEXTBOOK OF PEDIATRICS (19th ed. 2011) ["NELSON'S "] at 536-37.

[20] She initially failed the audiological evaluation; however, upon re-testing, her hearing was found to be within normal limits. Pet. Ex. 3, pp. 13-15.

[21] On September 17, 1999, A.A received her first vaccinations, which included the combined diphtheria, tetanus, and acellular pertussis ["DTaP"]; Haemophilus influenzae Type b ["Hib"]; and the inactivated polio ["IPV"] vaccines. Pet. Ex. 9, p.1. She received the second round of the same vaccines at her two month well child visit on November 19, 1999. *Id*. She received her third DTaP and Hib vaccines at her six month well child visit on January 21, 2000. *Id*. She received the varicella and her first hepatitis B vaccines at her one year well child visit on July 26, 2000. *Id*.

[22] A.A. was evaluated by a variety of health care professionals at Countryside Pediatrics, including medical doctors, certified pediatric nurse practitioners, and registered nurses. These professionals will all be referred to as her "pediatrician," regardless of their credentials.

[23] A.A.'s pediatrician made use of developmental checklists with very specific developmental milestones for specific ages. Those for the two month visit incuded: (1) Regards face directly; (2) Lifts head when upright; (3) Coos; (4) Smiles; (5) Grasps object when placed in hands; (6) Responds to sound. Pet. Ex. 9, p. 13.

On November 11, 1999, at about four months of age, she was seen for an upper respiratory infection ["URI"]. Pet. Ex. 9, p. 62. She had awakened screaming, with fever, irritability, and loss of appetite. *Id.* Her pediatrician gave instructions to call if her fever exceeded 100 degrees or if she did not improve within three days. *Id*. On November 16, 1999, she was seen due to congestion, irritability, and difficulty sleeping, and was diagnosed with bronchiolitis. *Id*., p. 61. She returned again on November 19, 1999, with URI symptoms and continued congestion. *Id*., p. 60.

At her six-month well child visit on January 21, 2000, A.A.'s growth and development were normal. Pet. Ex. 9, p. 12. The medical report indicated a normal physical examination, and normal development as measured by eight defined skills, including whether she laughed and babbled or could sit with little support.[24] *Id.* On January 26, 2000, she returned due to a persistent cough and runny nose, which was diagnosed as a URI. *Id.*, p. 59. She had been pulling at her ears, as well. *Id.*

A.A. was seen for her nine-month well child visit on April 21, 2000. Pet. Ex. 9, p. 11. The medical report contained no written comments, but indicated a normal physical examination, and normal development as measured by seven defined skills, including the ability to imitate "mama, dada."[25] *Id.* On April 26, 2000, A.A. returned due to congestion and a raspy voice. *Id*., p. 58. After examination, she was diagnosed with right otitis media ["OM"], bilateral conjunctivitis, and a URI. *Id*.

On July 24, 2000, A.A. attended her one-year well child examination, accompanied by her nanny. She was assessed as normal with regard to illness and accidents, and her temperament, as reported by the nanny, was "no problem." The corresponding medical report indicated a normal physical examination, and normal development as measured by eight defined skills, including whether she could walk two to three steps or say one to three words.[26] Pet. Ex. 9, p. 10.

B. Administration of Allegedly Causal Vaccination.

As reflected by the medical evidence of record, A.A. did not visit any healthcare provider between her one-year well child visit and her 15-month checkup. At that examination, on October 23, 2000, she was tugging at her ears and was reported to often have a cold. Pet. Ex. 9, p. 9. Her physical examination was normal, although her tympanic membranes had fluid. *Id.* She also had normal development as measured by

[24] The eight assessed developmental skills were: (1) Reaches for toys; (2) No head lag; (3) Laughs, babbles; (4) Peak-a-boo, pat-a-cake; (5) Sits with little support; (6) Fearful of strangers; (7) Rolls over; (8) Bears own weight. Pet. Ex. 9, p. 12.

[25] The seven assessed developmental skills were: (1) Pincer grasp; (2) Holds bottle; (3) Imitates mama, dada; (4) Peak-a-boo, pat-a-cake: (5) Sits well alone; (6) Crawls; (7) Pulls up to stand. Pet. Ex. 9, p. 11.

[26] The eight assessed developmental skills were: (1) Precise pincer grasp; (2) Stands alone; (3) Walks 2-3 steps; (4) Says 1-3 words; (5) Imitates sounds; (6) Eats and drinks sitting up; (7) Points; (8) Waves "bye-bye." Pet. Ex. 9, p. 10.

five defined skills, including whether she could walk well alone and point at one to two body parts.[27] *Id.* At this examination she received her first MMR, second hepatitis B, and fourth Hib vaccines. *Id*., p.1. Petitioners claim this MMR vaccine was causal of A.A.'s current condition.

C. Growth and Development Following the October 23, 2000 Vaccination.

The first reported illness following her 15-month check-up and MMR vaccination was nearly two months later, on December 18, 2000, when she was treated for a viral infection and early OM. Pet. Ex. 9, p.57. The examination report from that encounter reflected that A.A. had vomited the previous night, and awakened with a fever; however, there is no mention of any behavioral or developmental concerns. *Id.* On January 25, 2001, she was treated at the Loudon Healthcare Emergency Room for second degree burns to her hands after she touched a hot fireplace screen at home. Pet. Ex. 22, pp. 18-20.

A.A. was seen for her 18-month[28] well child visit on March 1, 2001. Additionally, she had a runny nose and was teething. The examination report noted that the burns to her hands were healing well. Some issues with the previous nanny were reported, but A.A. was "opening up more" now with a new nanny. Her physical examination was completely normal, except for a left ear infection. She was prescribed an antibiotic, with orders to follow up in 10 to 14 days. She was behind on two vaccinations (DTaP and IPV), which could be administered at the follow-up visit. Her development was again measured against a defined set of skills; for the first time, A.A. did not display some of the expected skills. The report indicated that she was fully able to drink from a cup, walk up steps, point to body parts, and scribble. However, she had not mastered using a spoon and only took off some clothes. Her ability to build three to four block towers was not checked as achieved. And, the response to whether she could speak 4-10 words was "? consistency." Despite diagnosed acute left OM, she was evaluated as a "well 19 month old." Pet. Ex. 9, p. 8.

A note dated March 1, 2001 continued the report from A.A.'s 18 month well child visit. It stated:

> Mom reports [decreased] language skills. Baby seems to understand [but] sometimes refuses to talk/play games. Mom attributes above to change in nanny – mom wasn't pleased with nanny. Also child burned hand in [January 2001]. New nanny seems knowledgeable [about] child dev[elopment]. Takes [baby] to play groups, library, reads & sings, etc. Mom to continue to talk to baby, play games, read & sing – but to back off

[27] The five evaluated developmental skills were: (1) Drinks from cup; (2) Walks well alone; (3) Crawls up steps; (4) Rolls and tosses ball; (5) Points at 1-2 body parts. Pet. Ex. 9, p. 9. Language or vocabulary was not assessed on the examination record, but the Denver II developmental screening form reflected that she had at least three words at 15 months of age. *Id*., p. 7

[28] A.A. was more than 19 months old at the time of the visit.

> if this becomes a power struggle [with baby]. [Follow up] if concerned or if not seeing progress in language dev[elopment] over [the] next 2 months.

Pet. Ex. 9, p. 18.

The examiner also completed the medical portion of the Virginia School Entrance Health Form, which was required prior to A.A.'s admission to school. The report generally mirrored the findings noted in the Countryside Pediatrics record described above and estimated her developmental level to be within normal limits. Pet. Ex. 7, p. 13.

A.A. next visited Countryside on March 23, 2001, due to coughing and congestion. Also of concern was a reported increase in hearing loss after the "past 3 [bilateral] OM" and her ear tugging. She was diagnosed with a URI and bilateral OM. A note indicated that A.A.'s "language skills [were] improving" and that she could say "uh-oh" and "bye, bye." Pet. Ex. 9, p. 56.

Several weeks later, on April 2, 2001, A.A. was treated for OM. She had continued tugging at her ears, was "generally feeling miserable," and had been "sleeping a lot." Pet. Ex. 9, p. 55. She also received her third hepatitis B and IPV and her fourth DTaP vaccines at this examination. *Id.*, p. 1.

On May 7, 2001, A.A. returned to follow up on her three ear infections, accompanied by her nanny. The examination report noted concerns regarding A.A.'s hearing, speech/language delay, and vocabulary of about six words. She was diagnosed again with OM. For the first time, her pediatrician assessed her as developmentally delayed in speech. Pet. Ex. 9, pp. 19, 54; *see also id.*, p. 7 (Denver II).[29]

A.A. was next seen on June 13, 2001, for a possible urinary tract infection ["URI"]. Her mother thought she was having problems urinating. She was noted as crying, but consolable at the appointment. Mrs. Allen was to call if the concerns persisted. Pet. Ex. 9, p. 53.

D. Diagnosis of and Evaluations for Speech Delay.

A.A.'s two-year well child visit took place on August 6, 2001. Her physical examination was normal. However, she was again diagnosed as having a developmental speech delay. The examination was "very difficult," because A.A. was

[29] The Denver Developmental Screening Test ["Denver II"] was a widely used assessment for examining the developmental progress of young children; however, in recent years the test has fallen out of favor with some early childhood organizations. *See, e.g.,* Minnesota Department of Health, http://www.health.state.mn.us/divs/fh/mch/webcourse/ devscrn/instrument.cfm (last visited Sept. 8, 2015) (not recommended as a developmental screening instrument). The test's publisher closed in 2015; the testing materials are no longer available for sale. *See* Denver Developmental Materials, Inc., http://denverii.com/ (last visited Sept. 8, 2015).

apprehensive and screamed throughout the encounter. As a result, the examination report, including the nine-item developmental skills checklist, was not thoroughly completed. The two skills that were evaluated ("2-3 word sentences" and "repeats words") were marked as abnormal.[30] She was referred for speech evaluation. Pet. Ex. 9, p. 4.

A hearing test on August 27, 2001, was inconclusive, and she was re-evaluated on August 31, 2001. Although testing was again incomplete because A.A. "was very active and crying," the obtained results suggested "normal hearing in at least one ear." The audiologist recommended A.A. undergo a speech and language evaluation. Pet. Ex. 5, p. 1.

That speech and language evaluation was conducted on September 5, 2001. A.A.'s nanny accompanied her to the appointment and served as the informant regarding her daily communication skills and behaviors. Her parents supplied a written history. The report noted that A.A.'s medical history was significant for ear infections. Her developmental milestones were reportedly age-appropriate. Although she was clumsy with walking, she was able to run and climb with coordination. Her fine motor skills were still developing. Pet. Ex. 5, p. 4. Her speech and language landmarks were reported "as age appropriate to a point." *Id*., p. 5. She reportedly spoke "her first word 'Quack' at 1 year and [spoke] a little more/using animal sounds at 15 months." *Id*. However,

> [s]he stopped speaking after having 3 ear infections in a row.[31] She has just begun to put 2 words together. She has an estimated expressive vocabulary of 30 words. In the past 6 months she has begun to babble a lot again. She cries, points, and tugs, as her primary means of communicating with her parents and nanny. She does not communicate with peers. [She] reportedly will learn new words, but when she does, . . . previous learning is lost.

Id.

After testing and examination, the speech-language pathologist provided the following assessment:

> [A.A.] is an attractive young child who would not engage with this examiner. Based on clinical observations and caregiver's report, she presents with delayed receptive language skills and gaps in her expressive language development. Of greater significance are her poor pragmatic skills (eye contact, joint attention, etc.) and atypical behaviors:

[30] The nine assessed developmental skills were: (1) Uses spoon well; (2) Eats using spoon; (3) Walks up steps; (4) Knows name; (5) Runs without falling; (6) Builds 5-6 blocks; (7) 2-3 word sentences; (8) Repeats words; (9) Can do simple tasks. Pet. Ex. 9, p. 4.

[31] A.A. was seen for these ear infections on March 1 and 23, and April 2, 2001. Pet. Ex. 9, pp. 8, 54-56.

> preference of objects over people, sustained odd play, tantrums, resistance to changes in routine, showing distress for reasons not apparent to others, lack of response to verbal cues (although hearing tests in normal range), aloof manner, fascination with venetian blinds/lights, desire to hold objects daily, and walking on tip toes. These combined behaviors may suggest that she is experiencing more than just a developmental delay.

Pet. Ex. 5, p. 11. The speech pathologist "suspect[ed] autism" and recommended that A.A. "receive evaluation from a pediatric neurologist and/or developmental psychologist to assess communication and behavioral patterns to determine/rule-out underlying problems." *Id.*

E. Autism Evaluations.

On September 16, 2001, A.A. was seen for a neurologic consultation with Dr. Bennett L. Lavenstein at Children's National Medical Center ["Children's Hospital"], in Washington, D.C. In the resultant report, Dr. Lavenstein noted that A.A. had been referred by a speech pathologist who perceived "features of autism" in some of her behaviors. Pet. Ex. 9, p. 96. He recounted that A.A., by history, had

> [d]emonstrated normal behavior in the neonatal course. Subsequently sat, walked and was appropriate in her milestones . . . . In October of 2000 she had some oral sounds but then subsequently regressed. There has been some evidence of echolalia. Occasional stereotype movements have been noted, especially when excited with some hand motions, and she is noted to walk on her tip toes. At this time, she has been evaluated in a hearing evaluation with an audiogram that was noted to be normal. She has no history of seizures. There has been no evidence of regression.
> . . .
> Additional behavioral features reveal that [A.A.] frequently will stare at lights, stares in the mirror and continues to twirl her hair. She does have some interaction with those in the environment.

Id.

Her neurologic examination was generally within normal limits, but A.A. was non-communicative.[32] Pet. Ex. 9, p. 96. According to Dr. Lavenstein, A.A. was "a patient in whom there may have been development of primitive speech then a regression of speech, . . . a child who has autistic symptomatology." *Id*. He recommended an additional MRI scan and electroencephalogram ["EEG"] testing to determine whether

[32] Reflexes were normal, and she was not hypertonic.

"there are features that would be suggestive of the Landau-Kleffner syndrome." *Id*., pp. 96-97.[33]

Following the neurologic consultation, A.A. underwent further diagnostic testing, including a cerebral MRI and an EEG, as well as blood plasma analysis to obtain amino acid levels. A radiological report dated October 3, 2001, indicated A.A.'s cerebral MRI results were unremarkable. Pet. Ex. 4, p. 76. Similarly, an October 15, 2001, report indicated that her EEG results were within normal limits. Pet. Ex. 9, p.93. With regard to her amino acid levels, an October 22, 2001, laboratory report showed "mildly elevated" tyrosine and lysine, and "borderline high" branched-chain amino acids. The report stated, however, that clinical correlation was required, and Dr. Lavenstein indicated they were reported as "non specific" by Dr. Mendel Tuchman, who interpreted them. Pet. Exs. 10, p. 6; 9, p. 85.

On October 27, 2001, A.A. presented to Loudon Ear, Nose & Throat Specialists for an evaluation of her recurrent episodes of otitis media. During the consultation, A.A.'s mother reported that "[o]ver the last 10 months, [A.A.] ha[d] had 4-5 acute [otitis media] episodes, . . . and, more importantly, ha[d] been diagnosed with speech delay." Pet. Ex. 9, p. 92. According to her mother, A.A.'s "regression began when the ear infections started, and at least some of the developmental delay experts have indicated that the fluid in her ear and/or recurrent acute infections could be at least part of the problem." *Id*. The physician examined A.A. and confirmed that she suffered from a speech delay, "since at this age she still has very minimal vocabulary." *Id*. She opined that "her history of recurrent acute otitis media could be contributory since even transient conductive hearing losses would affect her speech development at this age." *Id*. The physician recommended bilateral myringotomy and ventilation tube placement. *Id*. The procedure was performed around October 2001.[34]

A.A. was seen repeatedly over an approximately six week period, beginning in November 2001, for minor illnesses, which included pharyngitis and otitis media. *See* Pet. Ex. 9, pp. 43, 45, 47, 49, 51. Reports of behavioral issues were mentioned during these visits. *Id.*

On the morning of December 17, 2001, A.A. was taken to the Inova Fairfax Hospital Emergency Department because of severe pain in her abdomen and groin area with recurrent bouts of uncontrollable crying and screaming, all of which had begun approximately one week earlier. Pet. Ex. 4, p. 10. After an initial examination, the emergency department physician rendered a tentative diagnosis of intermittent abdominal pain, rule out intussusception and UTI. *Id*. A barium enema and a kidney, ureter, and bladder ["KUB"] workup were negative for intussusception, but notable for

[33] This evaluation also appears at Pet. Ex. 10, pp. 17-18. Duplicates of other exhibits also appear in A.A.'s primary care records. I will not identify duplicate citations.

[34] Medical records of the procedure were not filed; however, the surgery appears to have occurred around October 2001. *See* Pet. Ex. 9, p. 92 (Oct. 27, 2001 audiology consult recommending procedure "in the near future"); Pet. Ex. 4, p. 28 (Dec. 17, 2001 medical history noting "PE tubes placed ~ 3 mo ago.").

increased stool in the colon, which "[t]he patient was not able to evacuate." *Id*., pp. 40-41. The emergency department recommended that A.A. be admitted to the hospital for further testing and evaluation. *Id*., p. 34. A.A.'s pediatrician was informed of her status and of the available test results, including evidence of thrombocytosis and increased C-reactive proteins ["CRP"]. Pet. Ex. 9, p. 41. All other tests were negative, but an upper gastrointestinal ["UGI"] was still needed. *Id*.

At admission, A.A.'s mother completed a comprehensive pediatric history form regarding her health and development. Pet. Ex. 4, pp. 56-58. She reported that A.A. was generally healthy, but noted that she had recently been sick, had allergies to eggs and dairy, and was "slightly behind" in meeting developmental milestones. *Id*. She specifically denied that A.A. had any history of gastrointestinal or genitourinary issues, or had any ear problems. *Id*. A.A.'s current medications were listed as Tylenol, smart oil, good bacteria, and unidentified supplements. *Id*., p. 56.

Additional history was provided to the attending physician during the admitting examination: A.A. was reportedly in her usual state of health following a flu-like illness when she developed increased fatigue, fussiness, and episodes of abdominal and perineal pain. Her symptoms were accompanied by extreme tantrums, during which she placed her hands near her perineal/paravaginal area and screamed uncontrollably. The episodes, which started about one week earlier, occurred several times per day and lasted for 20-30 minutes. Pet. Ex. 4, p. 28; *see also id*., p. 18 (pediatric history taken by resident).

As for her earlier medical history, the attending physician recounted her burn injury in January 2001 and a history of multiple ear infections requiring a myringotomy in October 2001. Pet. Ex. 4, p. 28; *see also id*., p. 18. The physician also noted that A.A. had undergone an EEG and MRI in October 2001 with normal results "per Dr. Lavenstein." *Id*., p. 28. Concerning her development, the physician reported that A. A. had a language delay and toe walked, but noted that she "runs [up and down] stairs, self feeds, [and] can speak in sentences, but talks little." *Id*. Her speech reportedly had increased after her myringotomy. *Id*. No history of behavioral problems was reported. *Id*., p. 18. With regard to her diet, the physician noted that A.A.'s food allergies were discovered by way of a home ELISA [enzyme-linked immunosorbent assay] test administered by her parents. *Id*., p. 28. A.A. was currently "followed by a nutritionist" and had a diet free of dairy and eggs and supplemented with vitamins. *Id*.

A.A. remained in the hospital overnight and was discharged on December 18, 2001. Pet. Ex. 4, p. 7. A hospital pediatric consultation report dated that day summarized the results of various tests undertaken during A.A.'s hospitalization. The consulting physician stated:

> [A.A.'s] work up so far has included a [KUB x-ray] which is notable for increased stool in the colon as well as a normal barium enema and normal pelvic ultrasound with Doppler. Of note, she does have thrombocytosis with platelets of 947 and mildly elevated CRP of 1.32. Mild anemia with

> hemoglobin of 11.2[,] but with normal electrolytes, liver function tests and urinalysis. An electroencephalogram being done today . . . is pending.[35]

Pet. Ex. 4, p. 21.

The consultant noted that A.A.'s physical examination was normal and stated that "[a]t this point, it is unclear if her colicky pain is clearly gastrointestinal related or not. It is possible that she may be having some post infection enteropathy which is worsened with her constipation." Pet. Ex. 4, p. 21. He recommended an upper GI examination to "rule out malrotation with intermittent volvulus and ischemia," additional blood work, and continued Milk of Magnesia "to clean her out." *Id*. The upper GI study performed the following day, December 19, 2001, was negative for any abnormalities, including malrotation or duodenal obstruction. *Id*., p. 5.

On December 20, 2001, A.A was seen at Countryside for repeat blood testing. The medical report noted that A.A. was feeling better. Pet. Ex. 9, p. 39. However, on December 31, 2001, A.A.'s mother telephoned Countryside seeking an appointment. She reported that A.A. was "hysterical, upset since [2:30 a.m.], throwing things." She stated that A.A. had been "evaluated at Fairfax Hospital [two] weeks [earlier] for these same symptoms, EEG done, upper and lower GI, barium enema done, no cause was found." *Id*., p. 37. An appointment was scheduled for later that day. The corresponding medical report noted that A.A.'s mother requested a toxicology workup for metals and expressed concern about her decreased language ability. The possibility of autism was raised. *Id*., p. 36.

On January 3, 2002, A.A. was evaluated by a gastroenterologist for constipation. The consultation report recounted that A.A. had recently been hospitalized "for extreme episodes of rage/irritability." Pet. Ex. 9, p. 90. It noted that neurological evaluation was in progress "for possible developmental disorders." *Id*. Abdominal x-rays taken during hospitalization "revealed large amount of retained stool" and the upper GI study was normal. *Id*. The physician conducted a physical examination with normal findings. *Id.* A diagnosis of constipation was made. *Id.*

On January 14, 2002, A.A.'s parents telephoned Countryside to discuss her status. During the call, A.A.'s father stated "that he [was] 100% sure that [A.A.'s] problems [we]re from her MMR immunization.[36] Her behavior started 30 days post

[35] The EEG results were normal. Pet. Ex. 4, p. 39.

[36] On January 28, 2002, Mrs. Allen was interviewed by a Loudon Public Schools social worker who was preparing a sociocultural assessment as part of A.A.'s application for special education services. During the interview she reported that A.A.'s "development was fine until 10-23-00 when she had her MMR vaccination." Pet. Ex. 8, p. 47. However, a few days later, on February 1, 2002, Mrs. Allen reported to a school psychologist that A.A. "was very outgoing and her language skills were developing within normal limits" until "[a]bout a year ago," when her "speech skills began to regress and she began to struggle in social situations." Pet. Ex. 8, p. 27. This time frame coincides with her three ear infections, which occurred in March and April 2001. *See* Pet. Ex. 9, pp. 8, 54-56.

MMR." Pet. Ex. 9, p. 35. He had been doing his own research on the Internet and had ordered several dietary supplements, including pills to improve brain function and help the body eliminate harmful metals.[37] *Id*. He also stated that they had seen a nutritionist named Kelly Dorfman who gave them "smart oil" to improve A.A.'s intelligence by 15 percent. *Id*.

On January 14-15, 2002, Dr. Lavenstein administered a 24-hour DigiTrace EEG to record A.A.'s brain activity. The corresponding report noted that A.A. had "a history of seizures. First episode was December 2001 and last episode was [January 13, 2002]. They seem to occur every day. Patient has a history of speech delay. These [seizures] appear to be temper tantrum-like events." Pet. Ex. 10, p. 1. Doctor Lavenstein stated that the EEG recorded several of these tantrum events, but "[a]t no time was there any evidence of a[n] electrographic seizure correlate." *Id*. The EEG revealed "no premonitory electrographic discharge" or "evidence of any focal epileptiform disturbance." *Id*. His impression was: "This 24 hour EEG correlating with any temper tantrums does not reveal any evidence of paroxysmal abnormality and is within normal limits." *Id*.

In a letter dated February 2, 2002, Dr. Lavenstein provided his conclusions and recommendations in light of the various tests performed to date. With regard to her sleep problems, he advised that A.A. undergo a polysomnogram for further sleep analysis, as she had a sleep disorder. Pet. Ex. 9, p. 85. Concerning her developmental delays and behavioral problems, Dr. Lavenstein raised concern "about the possibility of autism," as there was "past development of primitive speech, then regression of speech in the setting of a positive family history of epilepsy in a child who does have autistic symptomatology." *Id*. Neurologic testing showed no evidence of Landau-Kleffner syndrome, and an MRI scan was within normal limits. *Id*. Laboratory studies to date were basically normal, including an amino acid screen. *Id.* Although there "were some borderline levels of tyrosine and lysine[, t]hese were felt to be nonspecific[.]" *Id*. Dr. Lavenstein recommended that A.A. begin taking Klonopin to help her sleep. *Id.* He noted that A.A. was to see Dr. Zimmerman in the near future. *Id.*

F. Evaluations and Treatment at the Kennedy Krieger Children's Hospital.

On February 13, 2002, A.A. was evaluated by Dr. Gerald Raymond at the Neurobehavioral Unit of the Kennedy Krieger Institute in Baltimore, Maryland. Pet. Ex. 6, p. 25. The initial evaluation report noted that A.A.'s parents were concerned about her "loss of language and social skills, and frequent temper tantrums."[38] *Id.* According to her parents, A.A. "sat up independently at 6-months and walked by 12-months." *Id*. At the time of the evaluation, she was able to use a sippy cup, spoon, and a fork, "but

[37] Mr. Allen specifically identified the following websites: www.life-enhancement.com; www.extremehealth.com.

[38] Contemporaneous with the initial visit, A.A.'s parents completed a developmental and medical history form to provide background information for Dr. Raymond's evaluation. Pet. Ex. 6, pp. 39-44.

sometimes [ate] with her hands." *Id*. She also assisted with dressing and undressing, but was not toilet-trained. *Id*. The report continued:

> Loss of language skills was noted at approximately 16-months. Prior to that, she was reportedly able to make 'animal sounds' such as 'roar!' when asked, and was able to state her age. Parents feel that loss of skills was concomitant [*sic*] with her 15 month MMR vaccination. She has made some improvements since that time and is now able to count some objects. She occasionally uses words or phrases spontaneously, such as "daddy go look." She may say "French fries" when the family goes to McDonald's. She has made better eye contact recently, since starting dietary supplements.

Id.

With regard to her previous medical history, Dr. Raymond noted the placement of tympanostomy tubes due to frequent otitis media, and recounted her normal neurological evaluation in September 2001, and hospitalization for severe temper tantrums in December 2001. Pet. Ex. 6, pp. 25-26. He also noted that A.A. had been taking a dietary supplement, "which include[d] chelation with EDTA," for approximately three weeks.[39] *Id.*, p. 26. The supplement had reportedly improved her behaviors. *Id*. She was also prescribed Klonopin. *Id*.

Following physical examination with normal results, Dr. Raymond assessed A.A. as "a 2-year, 6-month-old child who has had regression of language and social skills by parental report." Pet. Ex. 6, p. 27. He noted that her "[l]oss of language could be suggestive of Landau-Kleffner's syndrome; however, multiple EEG studies done in the past have been normal." *Id*. Of specific concern were A.A.'s "poor pragmatic skills, limited eye contact, and stereotypies. These features, with a history of regression, are suggestive of autistic disorder. In her case, based on findings, Rett Syndrome should also be considered." *Id*. He recommended continued use of Klonopin to manage her behaviors, but cautioned use of the dietary supplement. *Id.* He also recommended karyotype, fragile X DNA, and Rett studies.[40] *Id*.

That same day, A.A. was seen by Dr. Andrew Zimmerman, a pediatric neurologist at the Kennedy Krieger Institute, for further evaluation of autistic symptoms. Pet. Ex. 6, p. 23. Dr. Zimmerman's report included the following history:

> The parents report normal development until 11/00, when she underwent regression 1-2 weeks following MMR immunization, with loss of language and eye contact as well as social interaction. She is currently undergoing

[39] Testing of A.A.'s hair reportedly had revealed "high metal content and arsenic." Pet. Ex. 8, p. 47.

[40] Fragile X genetic testing was normal. Pet. Exs. 6, p. 71; 15, p. 120. Rett syndrome genetic testing was normal. Pet. Exs. 6, pp. 72-73; 15, pp.121-22. Both tests were performed on February 14, 2002.

> vitamin therapy and 'GI support', and has had trace metal testing of the hair. She has been followed by Dr. Bennett Lavenstein and had normal EEGs, including an overnight study, and cranial MRI scan. She has shown increasing toe walking in recent months. Father feels her eye contact is improving since starting 'oral chelation', which is obtained through the mail. She uses up to 100 words inconsistently and tends to lose single words that she has once used. She is now sleeping through the night, though she has had episodes of awakenings every 2 hours, and will have rage episodes with hitting her head and pulling her hair.

Id.

A.A. reportedly had exhibited "repetitive behaviors, hair-twirling and echolalia." Pet. Ex. 6, p. 23. Doctor Zimmerman assessed "her rating on the Childhood Autism Ratings scale [as] 35-37, in the moderately autistic range." *Id*. He noted that there was no family history of autism, and A.A. was an only child. *Id*. He conducted a physical examination:

> On exam, [A.A. was] fussy and reactive, does not engage or sustain eye contact. Occasional word sounds [were] heard, as she responds to her parents and seeks their attention briefly, and they are responsive to her. . . . The cranium appears relatively small compared to the face, with large features, and head circumference [in the] 50th percentile . . . . Tone is moderate and symmetrical. She does not engage in a ball game, but reaches into the can to obtain one. She climbs up and down a set of steps repeatedly, has mild truncal instability but no tremor or movement disorder. . . . Toe walking is persistent and increases with an instability of her gait. The feet are plethoric in appearance (and are reported to change color from pink to blue at times without apparent cause). Brief hyperventilation episodes were reported on the exam earlier today.

Id.

Dr. Zimmerman concluded that A.A. "present[ed] an atypical history and appearance consistent with an encephalopathy and a pervasive development disorder (autism spectrum)." Pet. Ex. 6, p. 24. Because of her "history of regressive encephalopathy," he recommended genetic testing, as well as testing of quantitative plasma amino acids and urine organic acids. *Id.* He also recommended that she continue her treatment with Klonopin. *Id*.

On July 15, 2002, A.A. returned to Dr. Zimmerman for a follow-up appointment. During the visit, A.A.'s mother reported that she had experienced "an increase in language functions" due to her involvement in an infants and toddlers program, but had "lost some ground" after the program ended for the summer. Pet. Ex. 6, p. 21. Doctor Zimmerman noted that A.A. "ha[d] functional language, [but her] pragmatics [we]re still

poor and she [did] not readily engage or relate." *Id.* He planned to begin to taper her Klonopin dosage over the next few weeks. *Id*.; *see also id.*, p. 88.

The report indicated that urinary organic acids had not been obtained, but that "[g]enetic testing was normal, including chromosomes and DNA for fragile X. Rett syndrome genetic testing was normal. There is no family history of hearing loss or muscle weakness (mitochondrial disorder)." Pet. Ex. 6, p. 21. With regard to behavior, Dr. Zimmerman reported that "[s]he marche[d] around the room and [was] continuously active. She jump[ed] and ha[d] some hand flapping with excitement." *Id*. He stated that they again "reviewed the history of her loss of functions following MMR vaccine. She has regressive encephalopathy with development of PDD (autism spectrum disorder)." *Id*. He recommended that she have Applied Behavior Analysis ["ABA"] therapy.[41] *Id*.

In addition to ABA therapy, Dr. Zimmerman recommended additional testing, including "quantitative urinary organic acids, fasting serum lactic acid, serum chemistries with liver function tests (especially AST), as well as CK (CPK),"[42] in view of the possibility of mitochondrial disorder. Pet. Ex. 6, p. 21. He stated "[m]itochondrial disorders are difficult to diagnose, and some of them are responsive to specific vitamin therapies." *Id*. He noted at the conclusion of his report that A.A. "had normal quantitative amino acids, including the alanine/lysine ratio." *Id*.

On November 4, 2002, A.A. returned to Dr. Zimmerman for a follow-up visit. A nursing report noted that A.A. was non-compliant and crying during intake procedures. Pet. Ex. 6, p. 86. It also noted that she was being treated with vitamin therapy. *Id*. During the examination, A.A.'s mother reported increased sensory sensitivities and agitation since she stopped taking Klonopin. Pet. Exs. 6, p.19. But she noted that A.A. was "showing more responsiveness in her therapies and [was] using a few words." *Id*.

With regard to test results, Dr. Zimmerman noted that

> [l]aboratory testing again showed a normal amino acid profile. Her plasma lactate was 2.2 mM/L (0.7-2.1) and CPK was 196 IU/L (0-165) . . . and calcium 10.6 (8.5-10.4). She was struggling when the test was done and, by report, the tourniquet was not removed. These findings are further suggestive of a mitochondrial disorder but not clearly diagnostic.
> . . .
> We were able to obtain a urine specimen for quantitative organic acids that will be sent to Dr. Kelly's lab, and we also obtained a carnitine profile

[41] ABA therapy consists of the "application of learning theory based on operant conditioning" and "is the only intervention recommended by the Surgeon General" for ASD. *Dwyer*, 2010 WL 892250, at 272, n.650 (internal citations omitted).

[42] Blood chemistry results (Aug. 7, 2002). Pet. Ex. 6, pp. 69-70. Plasma amino acid results (Aug. 29, 2002). *Id.*, pp. 66-67.

> and will request repeat AST and CK determinations.[43] We will then begin a trial of carnitine (Carnitor) increasing as tolerated up to 500 mg or 5 cc t.i.d. . . . She will also take folic acid 0.5 mg daily. We will later consider addition of other vitamins to the regimen depending on results. We will also consider further evaluation for mitochondrial disorder with spinal fluid lactic acid and/or muscle biopsy. We also obtained a carnitine profile today.

Pet. Ex. 6, p.19.

Doctor Zimmerman prescribed carnitine and folic acid and ordered a follow-up in three months. The discharge diagnosis was "encephalopathy." Pet. Ex. 6, p. 85.

On November 15, 2002, A.A. was seen at Countryside due to a reported seizure that morning. Pet. Ex. 9, p. 2. The medical record reflects that A.A. had a "grand mal" seizure, which lasted approximately three minutes. *Id.* She was taken to Countryside on the advice of Dr. Zimmerman. *Id.* Physical examination was normal. *Id.* A.A.'s new "vitamin therapy" was mentioned. *Id.*, p. 24. On November 23, 2002, A.A. was treated for pharyngitis and viral infection. *Id.*, p. 23. She reportedly "missed school all week." *Id.*

On January 13, 2003, A.A. had another EEG, the results of which indicated "a focal cerebral disturbance of the right temporal region, but possibly involving the right cerebral hemisphere diffusely." Pet. Ex. 6, p. 54. The reporting physician noted "no clear epileptiform discharges," but could "not rule out an epileptic disorder." *Id*. He recommended an imaging study be performed "to evaluate for structural abnormalities." *Id*.

A.A. was seen at Countryside on January 21, 2003, due to another reported grand mal seizure that morning, which lasted about two minutes. Pet. Ex. 9, p. 22. The medical report noted that she was scheduled to see Dr. Zimmerman the following day, but that he wanted her to be seen at Countryside "because she ha[d] had 4 seizures since [the] new year." *Id.* Physical examination was normal, with the exception of an inflamed right tympanic membrane, diagnosed as acute OM. *Id*.

On January 22, 2003, A.A. returned to Dr. Zimmerman for a follow-up visit. Dr. Zimmerman discussed A.A.'s most recent EEG results and noted that she had had four "generalized tonic-clonic seizures, apparently nonfocal, over the past several weeks after starting a trial of Carnitor (L-carnitine), [which] was discontinued about 3 weeks ago." Pet. Ex. 6, p. 15. Although her last seizure occurred the previous day and she was presently alert, her mother observed "intermittent episodes of convergence spasm

[43] The report from the repeat testing noted these results as "CK = 201 IU/L (24-170); Calcium 10.7 [8.5-10.4]; AST 44 U/L (0-31); CO2=19; carnitine profile normal; organic acids – normal." Pet. Ex. 6, p. 19; *see also* Pet. Exs. 6, p. 56 (Johns Hopkins lab report dated Nov. 4, 2002); 6, p. 57 (KKI genetics lab report dated Nov. 7, 2002); 6, p. 58 (KKI mass spectrometry lab report dated Nov. 8, 2002).

of the eyes" during the "past week or so." *Id*. A.A.'s speech, however, had reportedly improved while taking Carnitor. *Id*.

Doctor Zimmerman noted a limited familial history of seizures, but stated that A.A.'s MRI films from October 2001 appeared normal, "showing no focal abnormalities on the right side." Pet. Ex. 6, p. 15. He recounted that she had "a history of normal development until about 2 weeks after her MMR immunization at 18 [*sic*] months of age. Up to that time, she knew her colors and was using words and was pointing. She began repetitive behaviors and declined in her speech production with her regression." *Id*. The seizures, however, were "a new onset." *Id*. This history is significantly different from the medical records showing A.A.'s skill level at the time of vaccination and from the histories provided before her parents asserted that the MMR vaccine was causal. *See, e.g.*, Pet. Ex. 9, p. 10 (pediatrician assessment at one-year checkup indicating A.A. knew one to three words); Pet. Ex. 5, p. 4 (parental report to speech-language pathologist on September 5, 2001, stating that A.A. spoke "her first word 'Quack' at 1 year and [spoke] a little more/using animal sounds at 15 months"), p. 5 (she "stopped speaking after having 3 ear infections in a row"); Pet. Ex. 9, p. 96 (parental report to Dr. Lavenstein on September 6, 2001, that at 15 months A.A. "had some oral sounds"; Dr. Lavenstein's characterization of her speech at that time as "primitive").

Doctor Zimmerman planned a repeat EEG in six weeks, after starting A.A. on Depakote. "Depending on the results of her repeat EEG . . . we may wish to repeat her MRI scan, if right sided or other focal abnormalities persist." Pet. Ex. 6, p.15. He also recommended updated bloodwork for "CBC, AST and a valproic acid level." *Id*. Any decision "to reinstitute treatment with carnitine and other 'mitochondrial vitamins'" would be determined at a later date. *Id*. Dr. Zimmerman prescribed Depakote and ordered a follow-up in six weeks. *Id.* The discharge diagnosis was, again, encephalopathy. *Id.*, p. 82.

Another EEG was performed on March 3, 2003, pursuant to Dr. Zimmerman's order. Pet. Ex. 6, p. 50. The record reflected "no seizure discharges or localizing signs" and was improved as compared to the one obtained on January 13, 2003. *Id*. The examiner also noted that "[t]he focal attenuation of activity noticed over the right side on the previous recording was not present in the current record; however, it must be kept in mind that there were fewer recording channels in the current record." *Id*.

That same day, A.A. was also seen by Dr. Zimmerman. He noted that A.A. was currently taking Depakote and had only "a single seizure [the previous] week after sleep deprivation and none ha[d] recurred." Pet. Ex. 6, p. 13. He also reported that "[s]everal studies suggest[ed] that [A.A.] has signs of a mitochondrial disorder." *Id*. As a result, he contacted Dr. Richard Kelley and asked him to review A.A.'s chart. *Id*. He intended to ask Dr. Kelley to see A.A. clinically "to review studies[,] comment on any further testing[,] . . . [and] recommend treatment." *Id*. In the meantime, Dr. Zimmerman started A.A. on coenzyme Q, folic acid, and thiamine; however, restarting Carnitor would be postponed "pending Dr. Kelley's recommendation." *Id*.

On April 8, 2003, A.A. was seen by Dr. Richard Kelley, a metabolic specialist at the Kennedy Krieger Institute, for further evaluation and recommendations for treatment. Pet. Ex. 6, p. 3. In his report, Dr. Kelley recounted A.A.'s relevant history, as provided by her parents and medical records. *Id.* Consistent with previous accounts, A.A. reportedly "did well in the neonatal period and appeared to be a healthy, thriving girl for the remainder of the first year." *Id.* "[L]anguage acquisition continued to develop normally up until the age of 15 months when, approximately one to two weeks after her MMR immunization, [A.A.] progressively lost most of her language, visual contact, and normal social interaction over several weeks." *Id*. Extensive testing and evaluation "to determine the cause of the losses [provided] no explanation for her autistic regression." *Id*. Then, in February 2002, A.A. was seen by Dr. Zimmerman. Although she had regained some of her language, "and to some degree, her socialization" by the time of the evaluation, "she continued to have major behavioral problems, including self-injury." *Id*. At that examination, she demonstrated "persistent toe-walking as well as some gait instability, suggesting . . . a primary neurological disorder and not idiopathic autistic spectrum disorder." *Id*.

In view of the "early regressive nature of [A.A.'s] pervasive developmental disorder and the abnormalities in [her] neurological examination, Dr. Zimmerman was concerned that [she] might have a metabolic disease or other genetic disorder causing her progressive developmental and neurological losses." Pet. Ex. 6, p. 3. He "obtained a number of basic laboratory studies for diagnosis of inborn errors of metabolism."[44] *Id*.

> These showed several abnormalities, including an increased plasma alanine level, increased ratio of AST to ALT, mildly increased creatine kinase level, mildly increased blood lactate level, and electrolyte evidence of a mild metabolic acidosis. Negative diagnostic testing for identifiable causes of autistic spectrum disorder included Fragile X testing, Rett syndrome mutation analysis, plasma carnitine profile, and urinary organic acid analysis. Taken together, the laboratory abnormalities suggested an inborn error of mitochondrial energy metabolism. Interesting with regard to [A.A.'s] having a possible mitochondrial disorder is that, although frank hypoglycemia has never been documented, [A.A.] seems to [be] very sensitive to fasting and, according her parents, 'melts' if she misses a between-meal snack. She also sometimes becomes 'stuporous' within 15 to 20 minutes of a meal and often wants to eat in the middle of the night.

Id.

In view of the "biochemical evidence for a mitochondrial disorder . . ., and because of success in treating similar children with pharmacological amounts of mitochondrial cofactors," Dr. Zimmerman had started A.A. on "stepwise supplementation with carnitine, thiamine, and folic acid[.]" Pet. Ex. 6, p. 4. A.A. became "very excitable and agitated on carnitine," however, and also experienced

[44] The report summarized the results of the diagnostic testing undertaken to date. Pet. Ex. 6, pp. 4-5.

several grand mal seizures. *Id*. Treatment with carnitine was discontinued and an anticonvulsant was prescribed. *Id*. With regard to the effectiveness of carnitine, Dr. Kelley noted:

> Although there was suspicion that the seizures had been brought on by treatment with carnitine, [A.A.'s] last seizure prior to initiation of anticonvulsive therapy occurred three weeks after stopping carnitine. After starting treatment with Depakote, [A.A.] . . . had no further seizures. However, [she] remains significantly more excitable and agitated than prior to initiation of any of these medications and supplements. As a result, [A.A.'s] parents suspect that some of [her] worsening behavior has been caused by Depakote. Also important is that [A.A] was noted to be much more alert and focused in school after starting treatment with carnitine, an observation that was made by teachers who at the time were unaware of [her] new medication.

Id.

Doctor Kelley noted that A.A. did not have a history of any significant illness or hospitalizations. Pet. Ex. 6, p. 4. It is not clear whether Dr. Kelley was unaware of her previous hospitalization for tantrums and constipation in December 2001, or whether he did not consider this event significant. He stated that "[a]part from the above history, [A.A. showed] no signs or symptoms of a metabolic disease such as food intolerance, chronic vomiting or diarrhea, recurrent infections, abnormal rashes, unusual odors, or decompensation with otherwise simple childhood infections (apart from the MMR immunization)." *Id*. He noted, however, that she "may have had more than the usual number of ear infections and has required frequent treatment with antibiotics as well as bilateral tympanostomy." *Id*. A complete physical examination was not undertaken, as the "visit was primarily for consultation regarding pharmacological treatment." *Id*., p. 5.

In his assessment, Dr. Kelley explained:

> Although autism in most children remains a diagnosis without known cause, [A.A.] . . . has many of the historical and laboratory characteristics that we now associate with a particular form of autistic spectrum disorder caused by an inborn error of mitochondrial metabolism. Children with this disorder (possibly a group of disorders), typically appear to be normal for their first 12 months or more before a viral illness or other stress[,] such as an immunization[,] provides the critical metabolic stress that sufficiently taxes or compromises energy metabolism in the brain to precipitate acute or subacute cognitive and motor deterioration. For reasons that most likely are explained by changes in neurotransmitter receptor densities in the brain, the period between 12 and 36 months is the time when children with these mitochondrial disturbances appear to be most susceptible to brain injury. Such injury may occur once or several times with additional stresses, or, more rarely, a child may regress for many months, even in

> the absence of specific stresses like infections or immunizations. Most likely because the greatest susceptibility for brain [*sic*] occurs during a peak period of language and social development, children who sustain this type of mitochondrial injury often develop signs of autistic spectrum disorder.

Id.

He then stated:

> In addition to historical information consistent with an inborn error of energy metabolism, [A.A.'s] laboratory studies are similar to those of other children with autistic spectrum disorders and mitochondrial disease, which for shorthand we call 'mitochondrial PDD.' These include a distinctly increased level of plasma alanine relative to essential amino acids, a high ratio of AST to ALT, mildly increased creatine kinase level, and mild metabolic acidosis. Although [A.A.'s] plasma lactate level was only borderline increased at 2.2 mM, the lack of a distinct lactic acidosis in children with mitochondrial PDD together with an increased alanine level is quite characteristic. This is also consistent with muscle biopsy studies in mitochondrial PDD children, which typically show a significant block at the level of complex I, the primary site of oxidation of pyruvate. Alanine, being the amino acid form of pyruvate, is secondarily increased, but more useful as a diagnostic marker because its degree of elevation can be expressed relative to other amino acids, and it is not subject to artifacts commonly encountered in doing pyruvate and lactate measurements. The mildly increased levels of AST and creatine kinase are presumed to reflect the involvement of muscle tissue, which, second only to the brain, has the highest demand for mitochondrial energy metabolism.

Id., pp. 5-6.

Doctor Kelley also discussed A.A.'s "hyperactivity reaction" to carnitine, which he explained was "not uncommon in mitochondrial PDD." Pet. Ex. 6, p. 6. With regard to her first seizure, he found it unlikely, "based on extensive international experience with carnitine treatment of metabolic disorders, that carnitine could be the primary cause of a seizure disorder, only the particular factor that demonstrates a child's predisposition to having seizures. Indeed, seizures are relatively common in mitochondrial PDD before any pharmacological treatments are begun." *Id*. Despite A.A.'s reaction, Dr. Kelley believed carnitine was beneficial and recommended A.A. restart the treatment. *Id*. In addition, he recommended "starting the combination of vitamins now commonly used in the treatment of mitochondrial diseases."[45] *Id*. The vitamin therapy was planned to continue "until at least age five years. *Id*. In the meantime, Dr. Kelley encouraged A.A. to "continue to be followed by Dr. Zimmerman and her developmental specialists to monitor her progress." *Id.* Although he found it unnecessary that she return for

[45] The vitamin mixture was coenzyme Q10, vitamins C and E, thiamine, and lipoic acid. Pet. Ex. 6, p. 7.

"continued formal evaluation" at his clinic, he offered to provide advice or consultation as necessary regarding adjustments to her medications. *Id.*, p. 7.

Finally, Dr. Kelley noted that although "the specific genetic lesion or lesions causing mitochondrial PDD" are not known, mitochondrial enzymatic analysis of muscle biopsies from "several similar children" have "almost always [shown] exactly the same biochemical profile." Pet. Ex. 6, p. 7. As a result, "undertaking an invasive and expensive muscle biopsy at this time would not seem to have any practical value." *Id.*

On July 14, 2003, A.A. returned to Dr. Zimmerman for a follow-up visit. He noted that she had been doing "remarkably well on the mitochondrial regimen" and provided a favorable evaluation. Pet. Ex. 6, p. 1. He reported:

> Today her eye contact is notably improved and she sustains it for several seconds and is briefly interactive. She plays with imagination with a toy stove and stays busy with it. She is heard to sing words clearly and is using single words and word combinations. Her sleep has improved, although she is up about once per week during the night and is 'wired' for a few hours. This is gradually improving. She has remained seizure free on Tegretol . . . . She still is having difficulty with transitions and sensory sensitivities. Her growth has improved with increase in weight . . . from 60th to 95th percentile, and height . . . represents increase from 50th to 75th percentile in the last four months.

Id.

Doctor Zimmerman noted that A.A.'s positive response to the mitochondrial regimen indicated a possible "underlying mitochondrial dysfunction which may be from a nuclear gene that affects the mitochondria." Pet. Ex. 6, p. 1. He ordered bloodwork and a follow-up in three months. *Id.*; *id*, p. 76; *see also* Pet. Ex. 15, pp. 98-99 (laboratory results).

On July 14, 2003, Dr. Kelly provided a letter excusing A.A. from further vaccination due to her condition. The letter stated that A.A. "has autistic spectrum disorder and biochemical evidence of a mitochondrial disease." It explained that "the physiological stress of a vaccine" can trigger the "onset of brain injury in children with mitochondrial disease . . . as was the case for [A.A.] at the time of her MMR immunization." For this reason, it was recommended that A.A. not receive any further MMR or cellular pertussis vaccines until she passed "the window of greatest vulnerability for brain injury," which in children with A.A.'s "type of metabolic disorder" is six years of age. Pet. Ex. 11, p. 162.

On October 27, 2003, A.A. returned to Dr. Zimmerman for a follow-up visit. The medical report reflected that A.A. "seem[ed] to be doing quite well on the mitochondrial vitamin supplements." Pet. Ex. 11, p. 160. She had been seizure free since January 2003, and the plan was to taper her off the anticonvulsant once she reached the two-

year point. *Id*. Laboratory results were generally within normal limits, including a comprehensive metabolic panel. *Id*.; *see also* Pet. Ex. 12, pp. 52-53.

On March 15, 2004, A.A. presented for a routine neurology follow-up with Dr. Zimmerman. According to her parents, A.A. had recently experienced a "regression" in her behaviors and skills. Pet. Ex. 11, pp. 155-56. She was having increased sensory integration problems, including frequent temper tantrums, and appeared less happy than usual. *Id*. Additionally, certain behaviors had returned or increased, including teeth grinding, stereotypic behaviors, humming, and toe walking. *Id*., p. 155. It had also become harder for her to transition to new situations and she was observed by her parents and teachers to be "more lethargic" and "less focused in the afternoon." *Id*., pp. 155-56. Of particular concern was a teacher report that A.A. had recently had a brief staring spell and "did not respond for a short time." *Id*., p. 155. Her father also reported observing a possible seizure-like episode, but was not certain. *Id*. Although A.A. "continue[d] to speak occasionally" and "respond to specific choices given to her, [she did] not make spontaneous speech." *Id*. She was "learning things," but her parents were considering her placement in "a special education kindergarten program where she w[ould] be pulled into regular programs in school." *Id.*, p. 156. It was noted that A.A. "ha[d] been on the mitochondrial vitamins for one year . . . with no change in the dosage." *Id*., p. 155.

The impression was that A.A. had undergone a regression in her behaviors and skills. Pet. Ex. 11, p. 156. The plan was to slowly increase her mitochondrial vitamins to their target dosage. *Id.* The possible staring spells were "concerning," so the plan was to increase her anticonvulsant medication. *Id*., p. 157. A follow-up was scheduled in three months. *Id.* Subsequent laboratory results were generally within normal limits, with the exception of creatine, AST, and her platelet count. Pet. Ex. 12, pp. 48-49. Her plasma carnitine was within normal limits. Pet. Ex. 12, p. 50.

On June 14, 2004, A.A. returned for a neurology follow-up with Dr. Zimmerman. The medical report reflected that A.A. had improved since the previous visit and "continued to do quite well on the mitochondrial vitamins." Pet. Ex. 11, p. 148. She was kept at her current levels, with no intention of ending the treatment "anytime soon, since they seem to be working very effectively." *Id*. Because she had been seizure-free for a year and a half, they planned to begin tapering her anticonvulsant medications. *Id*.

By December 2005, A.A. was off her anticonvulsant medication and doing well. Pet. Ex. 11, p. 135-36. In December 2008, Dr. Zimmerman planned to taper A.A. off of the vitamin cocktail to determine whether there was "still indication of mitochondrial dysfunction." Pet. Ex. 12, p. 1. Although it is not clear from the record whether this occurred, Dr. Zimmerman later wrote, in a June 21, 2010 evaluation, that A.A. continued to have "clinical suggestion of mitochondrial dysfunction."[46] Pet. Ex. 15, p. 1. As of the

[46] In his evaluation, Dr. Zimmerman noted: "When she was off all mitochondrial vitamins she seemed to regress and Father has noted that she improves after each morning dose of Carnitor[.] . . . Mother is not sure whether there is benefit from it, but agrees to continue with the treatment." Pet. Ex. 15, p. 1.

most current record, A.A. continued to take Carnitor and the mitochondrial cocktail. Pet. Ex. 64, pp. 1-2.

Petitioners submitted medical records dated through April 2012, at which time A.A. was 12 years old. The records reflected regular treatment with her pediatrician[47] and ongoing care with Dr. Zimmerman and others at KKI. Pet. Exs. 61, pp. 16, 18-20, 23-28, 30-31, 33-34 (Countryside Pediatrics); 15, pp. 1, 49-52 (KKI); 64, pp. 1-2 (KKI).

IV. Summary of Fact Testimony and Supporting Evidence.

At the July 10, 2013 hearing, A.A.'s father, James Allen, and her maternal aunt, Susan Edick, testified with regard to A.A.'s health and development prior to her October 23, 2000 MMR vaccination, and the changes they observed over the ensuing months. Mr. Allen and Ms. Edick provided additional evidence in the form of written affidavits. *See* Pet. Exs. 78, 79. Video and photographic evidence was also submitted. *See* Pet. Exs. 60, 75, 80, 81 (video); 76 (photos); Trial Exs. 1-3 (photos).

A. Mr. James Allen.

Mr. Allen testified that A.A. had a "healthy" birth and was regularly evaluated by her pediatrician, who expressed no concerns during her first year of development. Neither of A.A.'s parents had any concerns about her development either. Tr. at 6-7; Pet. Ex. 78 at 2.

A.A. reached a notable milestone just prior to her first birthday, when she took her first steps during a family vacation to the Outer Banks over the 4th of July holiday. Tr. at 7-8; Pet. Ex. 78 at 2. A photograph taken during the trip showed A.A. standing on the beach, smiling and playfully tugging on a rope attached to a boogie board.[48] Mr. Allen recalled that A.A. was happy on the trip, laughing and giggling. Tr. at 8; Pet. Ex. 78 at 2. He noted that "[o]nce she started walking, it wasn't long before she was running, too." Tr. at 8.

Early on, she also developed "a strong liking [for] the water" and enjoyed going to the swimming pool. Tr. at 9. Mr. Allen stated that they frequently took A.A. to a local swimming pool where she "would go in the wading pool and splash with other children." Pet. Ex. 78 at 3. One of her favorite places, though, was a large waterpark near their home. Tr. at 9; Pet. Ex. 78 at 3. He recalled that whenever A.A. visited the park, she was actively engaged with her surroundings—running, splashing, and playing with other children. Tr. at 9; Pet. Ex. 78 at 3. Her affinity for water was reportedly illustrated by a photo of A.A. with her mother in a pool.[49] The photo, which showed A.A. "kind of doing

[47] A.A. continued to suffer from recurrent OM.

[48] A photograph of the trip to the Outer Banks was used as Pet. Trial Ex. 1.

[49] A photograph of her swimming with her mother was used as Pet. Trial Ex. 3. Mr. Allen noted that A.A. was looking directly at the camera in the photograph. Tr. at 17.

the doggie paddle thing," was taken during "the summer of 2000, around her birthday." Tr. at 17.

With regard to her personality, A.A. was becoming "kind of a jokester." Tr. at 9. For example, when asked "how big" she was, A.A. would "smile, extend her arms and say 'Soooo big' and wait for everyone to laugh." Pet. Ex. 78 at 4; *see also* Tr. at 9-10. She could tell "knock-knock" jokes, too, although she "hadn't quite learned to hold back her laughter until the punch line[.]"[50] Pet. Ex. 78 at 3-4; *see also* Tr. at 10. She also loved animals and often played with the family's dogs. Tr. at 10; Pet. Ex. 78 at 5.

Mr. Allen testified that members of both sides of the family observed A.A. during her first year, and none expressed concern or reported any strange behaviors. Tr. at 11-12. Indeed, she "was actually accelerating, growing." Tr. at 12. According to Mr. Allen, she played well with other children, had no difficulty with eye contact, and responded when called to by name. Tr. at 10-12. She was "very social." Tr. at 11. In fact, by her first birthday, A.A. reportedly had learned to use "well over 100 words." Tr. at 70-72. In view of the other evidence regarding A.A.'s language at one year of age, this testimony cannot be accurate.

On her first birthday (July 21, 2000), A.A.'s parents threw a small party attended by family and friends. Tr. at 12-13. A photograph taken that day shows A.A. next to her birthday cake.[51]

In the fall of that year, over the Labor Day holiday, petitioners visited A.A.'s maternal aunt and family ["the Edicks"] at their home in Syracuse, New York. Pet. Ex. 78 at 3. Mr. Allen described A.A. as active during their stay and specifically recalled her playing croquet with him and several of her cousins in the backyard. *Id.* at 4. Although "she could only hit the ball about three feet, . . . she tried. She knew how to play. She understood the colors." Tr. at 33; *see also* Pet. Ex. 78 at 4. One of his memories was of her "saying she was 'a big girl' while holding the croquet mallet and trying to hit the ball." Pet. Ex. 78 at 4. A photograph taken that weekend[52] showed A.A. outside during a game of croquet, standing independently with a ball in her hands.

On October 14, 2000, the family visited a local pumpkin patch to purchase a few pumpkins. Mr. Allen recalled that A.A. was full of energy that day and enjoyed the experience. He specifically remembered her playing on playground equipment and

[50] This statement is simply not credible. At one year of age, A.A.'s pediatrician assessed her with having one to three words, which was considered to be normal development. Pet. Ex. 9, p. 10. Two to three word *sentences* were not expected until age two years. *See* Pet. Ex. 9, p. 4. Indeed, petitioners themselves reported that A.A. spoke her first word "quack" at one year and spoke "a little more/using animal sounds" at 15 months. *See* Pet. Ex. 5, p. 5.

[51] A photograph on her first birthday was used as Pet. Trial Ex. 2.

[52] Pet. Ex. 76; *see* Tr. at 115 (Ms. Susan Edick testified that she took the photograph on September 3, 2000).

helping to choose the pumpkins. Tr. at 19-20. "She was like a kid in a candy store, basically." Tr. at 21. Video from that day showed A.A. walking and touching the pumpkins.[53] In one segment, she was seen "pushing" a wheelbarrow while holding her mother's hand. Tr. at 20. Mr. Allen also thought she might have danced to some music playing in the background. Tr. at 21. His recollection from that activity was of A.A. "engaging with people, . . . with her mom and her dad, too." Tr. at 22.

Mr. Allen also videotaped A.A. at home on that same day in various situations—from running around the house to eating dinner.[54] In one clip, A.A. was standing in her crib looking at the camera. Mr. Allen described her as "a little grumpy" after having just awakened from a nap. Tr. at 15. In another, she was in the bathtub splashing and playing with some toys. Mr. Allen noted that she made eye contact and was "very interactive." *Id.* During her bath, A.A. was playing with a rubber ducky and splashed herself with water, "which she liked to do." *Id*. He recalled her saying "quack, quack" when asked what sound a duck makes, although the sound does not appear on the videos. Tr. at 15-17. She "loved to make animal sounds," but her "first words were da-da." Tr. at 15.[55]

After her bath, A.A. was videotaped playfully running around her parents' bedroom. *See* Pet. Ex. 60. When asked if she was vocalizing during the clip, Mr. Allen responded: "Yes. A little bit. Really she was kind of doing the quack-quack still after the bath, yeah." Tr. at 18. In a subsequent segment, she was engaged in a "game" with her father that involved her being chased "down the main hallway on the second floor." Tr. at 25. "That was a tickler bug thing . . . you know 'I'm going to get you[.]'" Tr. at 25. In the clip she also kissed her favorite stuffed toy—a teddy bear. Tr. at 26. In another scene, A.A. danced to a song playing on Sesame Street. Tr. at 28- 29. A later clip showed her seated in a high chair eating dinner. At the end of that clip she appeared to imitate her father. He explained: "I was doing the 'rah' and she was doing it back." Tr. at 29.

On October 23, 2000, A.A. received a MMR vaccination. Although Mr. Allen was present at the appointment, he could not recall any details. Tr. at 102-04. He did, however, remember noticing changes in her behavior following the appointment, but not necessarily on that day. Tr. at 73. He specifically recollected a developing awareness that something was wrong during a neighborhood Halloween party the family attended on October 29, 2000. Tr. at 77. The daytime, outdoor event included treats, games, and a participatory parade for the children to show off their costumes. Tr. at 30-31; Pet.

[53] Video of A.A. on October 14, 2000. Pet. Ex. 60.

[54] Video of A.A. on October 14, 2000. Pet. Ex. 60. Despite confessing his love for recording his daughter's life (Tr. at 14.), Mr. Allen was able to find video from only three events of her entire childhood. In view of his comments, I find the lack of other videos from holidays or birthdays in this period inexplicable and concerning for spoliation of evidence.

[55] This statement is contrary to earlier reports. *See, e.g.,* Pet. Ex. 5, p. 5 (reporting that her first word was "quack").

Ex. 78 at 4-5. She did not want to walk in the parade and displayed little interest in interacting with other children or participating in the activities. Tr. at 31; Pet. Ex. 78 at 4-5. She really "seemed inattentive and passive." Pet. Ex. 78 at 5. She "just stood in one place like a mannequin"—she "looked stoned." Tr. at 31. While there were "brief moments" when she "would take one step, two steps here, one or two steps [t]here," she did not really walk, and definitely did not run. Tr. at 36-37.

Mr. Allen contrasted this behavior with her actions over the Labor Day weekend, when she eagerly played croquet in her aunt's backyard. Tr. at 32-33. On that occasion, she was "interacting and playing games"—she wanted "to be like a big girl," to understand the rules and learn how to play. Tr. at 32-33. At the Halloween party, however, she did not play games, or want to walk, stand, or interact with the other kids. He recalled thinking that "maybe she's really shy or something."

In video taken during the neighborhood Halloween party, A.A. was seen standing with other children waiting for family and friends to take photographs of the group.[56] Tr. at 35. Mr. Allen recalled that afterwards A.A. just stood in place until every other child had left. *Id.* He thought she would want to follow them for the parade, but she did not. *Id.* Rather than walk, she allowed her mother to carry her for a while and then push her in a cart. *Id.* Mr. Allen observed the absence of eye contact or any sounds during the segment and noted that when they spoke to her, she showed no response. Tr. at 35-36. "You can hear the birds, but you don't hear her." Tr. at 36.

Her disinterest "was kind of startling" to him—"[i]t was a big change." Tr. at 37. In the past, she would have had "her hands in everything." Tr. at 38. But on that day she was not engaged. *Id.* As an example, he remembered that they tried without success to get her to play a beanbag toss game. *Id.* They "had to walk it up . . . and she'd put it through the hole and that was it." *Id.* The other children "sort of ran by her." *Id.* He remembered thinking "maybe she's got a bug or something or maybe she's just having a bad day." *Id.*

According to Mr. Allen, that day (October 29, 2000) marked the beginning of noticeable changes in A.A.'s behavior. Tr. at 38. From there she gradually stopped speaking and interacting, and her personality changed. *Id.*

That night, when she developed a fever and refused to eat, petitioners became concerned. Tr. at 78. Because her fever was over 100 degrees, they contacted A.A.'s doctor, who told them to administer Tylenol and to call back or come in if the fever did not subside. Tr. at 78-79. There is no record of this telephone call. The fever lasted four days, during which it "kind of spiked and . . . went down and spiked again." Tr. at 39-40. As a result of her illness, A.A. was unable to trick-or-treat on Halloween night. *Id.*; *see also* Tr. at 79-80 (testified that they contacted doctor twice); Pet. Ex. 78 at 5. They did not take her to the doctor. Tr. at 80-81.

[56] Video of A.A. on October 29, 2000. *See* Pet. Ex. 80, 81.

Mr. Allen stated that he and A.A.'s mother speculated as to the cause of the illness, but remained uncertain. Initially, they wondered if it was something she had eaten—perhaps too much candy or she had developed an allergy. Tr. at 40-41. They also considered that it was a "'bug,' like the flu[,]" or that she was maybe teething. As a new parent, the situation "was disconcerting." Tr. at 41; *see also* Pet. Ex. 78 at 5. However, this was not A.A.'s first illness.

According to Mr. Allen, A.A.'s behavior changed significantly after the fever. He stated that she was sleepy, cried at night, and wanted to go to bed early. Tr. at 81. She no longer was "talkative" and would not respond or make eye contact. Tr. at 41. She also stopped "watching Sesame Street and dancing." *Id*. Instead, she would sit on the carpet and pull pieces of thread. *Id*. She "wasn't mobile like other kids." *Id*. He could not recall, though, whether he or his wife contacted A.A.'s physician about her worsening symptoms. Tr. at 81-82; *see also* Tr. at 45.

Over the Veterans Day weekend in November 2000, the Edicks visited petitioners at their home in Virginia. Tr. at 42. During their visit, the two families made a trip to the National Zoo in Washington, D.C. *Id.* The zoo was A.A.'s "favorite place" because she liked animals—especially monkeys, which she previously had watched with fascination. Tr. at 42; Pet. Ex. 78 at 5. On this occasion, however, she was disinterested, and cried and fussed. Tr. at 43. Mr. Allen recalled thinking that "her behavior and lack of activity was because she was recovering from a bug." Pet. Ex. 78 at 5; *see also* Tr. at 43, 83. Because of her tantrums and crying, the trip was cut short. Tr. at 43; Pet. Ex. 78 at 6. "During this weekend," he also "noticed that [A.A.] seemed unsteady on her feet" and often "crawl[ed] to her destination." Pet. Ex. 78 at 5. She talked less, too. Tr. at 84. Petitioners did not take A.A. to the doctor, however. Tr. at 83-84.

Later that month, on Thanksgiving, the family gathered at Mr. Allen's grandfather's farm. Tr. at 43. At some point that day, Mr. Allen recalled talking to his mother about his concerns. Tr. at 44. He stated that she expressed concern, too, because A.A. was crawling more than walking. *Id.* She also seemed content to sit alone by herself. Tr. at 45; *see also* Pet. Ex. 78 at 6. This was noticeably different from her behavior on October 14th, when she was "running around, . . . interactive with other kids." Tr. at 45. In retrospect, Mr. Allen wished that he had called the doctor, but stated that other than reporting that he could not "get a great Kodak moment," he was not sure what he would have said. Tr. at 45.

Throughout the month of December 2000 "all [A.A.] wanted to do was sleep." Pet. Ex. 78 at 7. She also had frequent tantrums. Tr. at 86. "Her temperament changed from a child with a big personality to one who would only smile occasionally. Mostly, however, she stared off into space[.]" Pet. Ex. 78 at 7. On December 18, 2000, A.A. was seen by her pediatrician; however, Mr. Allen could not recall whether he attended or what was discussed. [57] Tr. at 84. Her behavioral problems continued to

[57] The medical record on December 18, 2000, reflects a diagnosis of early OM. Pet. Ex. 9, p. 57.

Christmas, which made the holiday a "disappointment." Tr. at 46. Petitioners stayed home for Christmas and were joined by A.A.'s maternal grandparents. *Id.* Although there were a lot of gifts, A.A. showed no interest in opening any of them on Christmas morning. Tr. at 46; Pet. Ex. 78 at 7. She even "cried when a gift was placed in front of her and left the room." Pet. Ex. 78 at 7. Mr. Allen remembered that she "still seemed sickly," having had an earache the prior week. Tr. at 46. Mr. Allen shot video on Christmas Day,[58] but noted that most of the clips showed "the good moments"—because "she was crying a lot," they had to reshoot numerous times. Tr. at 47-48. He remembered that she was miserable "[t]hrough the entire day all the way up to dinner" and was put to bed early. Tr. at 49. "For a kid on Christmas," her behavior was "kind of surprising." Tr. at 48. He contrasted her unhappiness with how she behaved on her birthday: "opening every little gift . . . and . . . going through the cake." Tr. at 50.

The day after Christmas, A.A. appeared to feel better, so petitioners tried again to get some "Kodak moments." Tr. at 50. However, despite being more cooperative, her behavior was still unusual. Though she showed increased interest in her toys, she did not play with them "appropriately." Tr. at 50. For example, one of the gifts was a set of toy kitchenware, which she banged against a nearby clock and stacked in piles instead of pretending to fix food. Tr. at 50-51. Mr. Allen stated that this was unusual—"before[,] she wasn't like that." Tr. at 51. "She was in a world of her own." Pet. Ex. 78 at 7.

After Christmas, A.A. "never really went back to where she was," and it was "years" before she started talking again. Tr. at 51. Petitioners eventually decided to seek the help of specialists, because they had received no "clear answers" from her treating physicians. Tr. at 52. He recalled the frustration he felt:

> I'm going to the pediatrician and they're treating her ear, they're treating her nose, they're treating her finger, they're treating her bellyache, they're treating her fever. They're treating symptoms; they're not treating the whole problem. . . . And you walk out and you feel better for about a half a day until you're home again.

Tr. at 52. However, the medical records reflect that A.A.'s pediatrician was actively engaged in her care and responsive to her parents' concerns.

On March 1, 2001, petitioners took A.A. to her 18-month well child visit. Tr. at 86. Although he could not remember anything specific about the visit, Mr. Allen knew he was concerned about her loss of speech and eye contact. Tr. at 86-87. According to the pediatrician's notes of that visit, A.A. did not display some of the expected skills for a child her age, including the ability to speak 4-10 words. *See* Pet. Ex. 9, p. 8. It was noted that there had been "problems" with the previous nanny, but that A.A. was "opening up more" with the replacement. *Id.* The record indicated that Mrs. Allen[59]

[58] Video of A.A. on December 25, 2000. Pet. Exs. 74, 81.

[59] The medical records of this visit do not indicate whether Mr. Allen was present.

expressed concern over A.A.'s language skills, noting that she "seems to understand [but] sometimes refuses to talk/play games." Pet. Ex. 9, p. 18. Mrs. Allen attributed this to the previous nanny, with whom she was not pleased. *Id.* The pediatrician advised Mrs. Allen to follow up if concerned or not seeing progress in language development over the next two months. *Id.*

On Easter, April 15, 2001, the family visited Mr. Allen's sister at her home, also in Virginia. Pet. Ex. 78 at 7. Mr. Allen remembered family members noting a "dramatic change" in A.A.'s behavior from when they saw her on her birthday and at Thanksgiving. *Id.* His sister, for instance, noticed that A.A. would not respond when called to by name. *Id.* at 8. Eventually his sister became "so concerned" about the changes she saw, that she and A.A.'s mother jointly called A.A.'s pediatrician "to see if [she] had lost her hearing." *Id.* About this time, A.A. also "began tip toe walking and hand flapping," as well as humming and pacing back and forth. *Id.*; *but see* Tr. at 87 (toe walking began "later in the year of 2001"; and the hand-flapping did not become "prevalent" until "around the Children's Hospital time frame" in September). To those who knew her, it was "becoming increasingly apparent that something was wrong." Pet. Ex. 78 at 8.

On April 24, 2001, Mr. Allen completed an application for A.A.'s admission to the Village Green Day School. Tr. at 87-88. On the application, he reported that his daughter did not have temper tantrums and noted no physiological, behavioral, or developmental problems or difficulties, including in the areas of speech, hearing, and mobility. *See* Pet. Ex. 7, pp. 7-8. He did mention, however, that she had a tantrum on a seven-hour family trip to New York. *Id*. When asked to explain his responses, he stated: "I was a first-time parent. I didn't see my daughter as having problems. I didn't see her as abnormal. I didn't know if any of these behaviors were normal or abnormal. So that's probably why I wrote that." Tr. at 90. He also noted: "At that point in time, no doctor had told me that there was anything wrong with her."[60] Tr. at 91.

In late August and early September 2001, A.A. was examined at Blue Ridge Speech and Hearing for a suspected hearing problem related to her recurrent OM. The resultant examination report noted that A.A. had reportedly "said her first word 'quack' at one year and [spoke] a little more/using animal sounds at 15 months, [but] stopped speaking after having three ear infections in a row." Tr. at 92 (quoting Pet. Ex. 5, p. 5). When asked if this was accurate, Mr. Allen clarified that A.A. "began to stop speaking in between each ear infection – that sentence reads as if after the three ear infections, she stopped speaking." Tr. at 93. Instead, "she had three ear infections as her language skills were deteriorating." Tr. at 93. The report concluded with a tentative diagnosis of autism. Tr. at 53; *see also* Pet. Ex. 78 at 8-9.

[60] This report may be technically correct in that a diagnosis of speech/language delay was not made until May 2001, but it was clear from the March 1, 2001 well child visit that A.A.'s mother had concerns about her development, and said that she refused to talk and play games. Pet. Ex. 9, p. 18

According to Mr. Allen, he and his wife were surprised by the diagnosis—in fact, it was the "first time" that he had heard the word "autism." Tr. at 53. He recalled staying up every night, reading "about autism until 3 or 4 in the morning. During those hours, [A.A] would wake up screaming and the only thing that would calm her down was watching cartoons with music in our bedroom." Pet. Ex. 78 at 9; *see also* Tr. at 96, 98-100.

On September 6, 2001, petitioners consulted with Dr. Lavenstein, a neurologist at Children's Hospital in Washington, D.C. Tr. at 55. He ordered additional testing, the results of which supported the ASD diagnosis. Pet. Ex. 78 at 10. Mr. Allen then "applied to get [A.A.] into Kennedy Krieger through a referral" and was successful. Tr. at 57; Pet. Ex. 78 at 10.

Additionally, during this period A.A. underwent a bilateral tympanostomy to treat her recurrent OM.[61] The procedure reportedly did nothing to improve her behavior—"she was still not responding." Tr. at 53. She was also taken to the Fairfax Hospital Emergency Department during the Christmas season in 2001 because of "one of [her] screaming episodes." Pet. Ex. 78 at 9. Testing revealed that she was "suffering from intestinal blockages. She was not digesting the food and it was acting like a poison in her body." Pet. Ex. 78 at 9. Petitioners eventually learned that A.A. had allergies to dairy and eggs—a condition commonly found in children with autism. Pet. Ex. 78 at 9.

When asked to identify the time frame in which he first connected the MMR vaccine to A.A.'s problems, Mr. Allen reported that it "was a slow gradual process of kind of putting one and one together and coming up with two." Tr. at 96. Although he could not say for sure, he thought it was "probably . . . late 2001." Tr. at 97. To assist his memory during testimony, Mr. Allen was shown a January 2002 medical record, which reflected his statement that he was "100 percent sure that [A.A.]'s problems are from her MMR immunization. Her behavior started 30 days post-MMR." Tr. at 97 (quoting Pet. Ex. 9, p. 35). In view of the record, Mr. Allen testified: "At that time, if I said I was 100 percent certain, I meant it." Tr. at 97.

In January 2002, petitioners were notified that A.A. would no longer be allowed to attend Village Green Day School due to behavioral difficulties. Tr. at 106. Mr. Allen recalled that "during that time frame . . . she was having the screaming fits." Tr. at 106.

In February 2002, petitioners met with Dr. Zimmerman for the first time. Tr. at 57. After an extensive workup, Dr. Zimmerman validated the ASD diagnosis. Tr. at 58. He then recommended that A.A. be tested for mitochondrial disorder to help guide her treatment. *Id.* Mr. Allen remembered that the testing, which involved obtaining a blood specimen, was very difficult because A.A. struggled against the procedure. Tr. at 58-59. After obtaining the results, Dr. Zimmerman informed petitioners that A.A. "tested positive for mitochondrial disorder" and referred them to Dr. Kelley for further testing and evaluation. Tr. at 59.

[61] *See* n.34, *supra*, dating the procedure as likely occurring in October 2001.

When petitioners met with Dr. Kelley, he confirmed that A.A. had a mitochondrial disorder and explained his recommended treatment was a "vitamin cocktail" that included Coenzyme Q10. Tr. at 61-62. Mr. Allen testified that after A.A. began the Dr. Kelley's prescribed treatment, her behavior slowly, but steadily improved. Tr. at 62-63; Pet. Ex. 78 at 10. Although she continued to toe-walk on occasion and have difficulty in social situations, other areas were positively changed. Tr. at 63. For example, she began to make eye contact, "her voice came back," she was better able "to conceptualize, particularly . . . in reading," and her confidence increased. Tr. at 63.

As of the time of the hearing, A.A. was, according to Mr. Allen, progressing in her development and doing well in school.[62] Tr. at Tr. at 63-68. Although her social skills were "not quite there," she was learning to interact with her peers and had made a friend at school; however, she was generally more comfortable around adults. Tr. at 63-64. He indicated that she still had stereotyped and repetitive motor mannerisms, but took medication to reduce these symptoms. Tr. at 65-67. She also continued to take "part of the cocktail." Tr. at 65.

B. Ms. Susan Edick.

Ms. Edick testified that she was employed as a special education teacher in New York State. Tr. at 108. She earned a Bachelor of Science in education and special education from Syracuse University and a Masters of Science in education from State University of New York in Cortland. Pet. Ex. 79 at 1-2. She was certified in New York State in "Special Education for Infants to Adults, Early Childhood Education, Elementary Education for Grades K-6 and Reading/Literacy Education for Grades K-12." Pet. Ex. 79 at 2.

According to Ms. Edick, her training included learning the signs and symptoms of various developmental disorders, including "emotional [and] learning disabilities and autism."[63] Tr. at 109. Two classes in particular focused on autism, with exercises on how to identify autistic behaviors and educate children with the disorder. Tr. at 109-10. She also studied normal growth and development in children of school age. Tr. at 109.

In the field of education, Ms. Edick worked as a K-4 resource teacher, performed student teaching in an early education program with special needs children, and taught special education children in an integrated co-teaching classroom. Tr. at 110. Some of her responsibilities have included test modification, evaluation and support of student Individualized Education Plans ["IEPs"], and identification and improvement of areas of weakness, such as "social behavioral" issues or a "learning disability in reading and writing." Tr. at 110-11. Over the course of her career, Ms. Edick has both taught

[62] Mr. Allen reported that A.A. was a "straight A" student in her program. Tr. at 64, 68. She was looking forward to attending high school the following year. Tr. at 68.

[63] It is unclear whether Ms. Edick had training and experience in identifying developmental disorders in pre-school-age children.

autistic children and been responsible for identifying those with autism spectrum disorder symptoms who might require intervention. Tr. at 111. She stated that in her work she might, for example, identify "learning disabilities or learning patterns in kids or serve on the committee for the school . . . [to] recommend further testing with a psychologist or with speech and language therapists or with specialists, ear, nose and throat, or doctors." Tr. at 111.

Ms. Edick testified that, as a close relative, she had frequent opportunities to visit petitioners and observe A.A.'s growth and development. Tr. at 112; *see also* Pet. Ex. 79 at 2. She also spoke often with A.A.'s mother—her sister—on the telephone. Tr. at 112. "[W]e would discuss different activities, what was going on with them in life or family." Tr. at 112.

Though she did not attend A.A.'s first birthday party, she remembered seeing A.A. when petitioners visited over the Labor Day weekend in September, when she was almost 14 months old. Tr. at 112; *see also* Pet. Ex. 79 at 2-3. According to Ms. Edick, A.A. seemed "very happy, very healthy" during their stay. Tr. at 113. From what she observed, A.A. "seemed very normal, [with] typical development for a child socially, cognitively, physically. She was walking. She was talking, typical vocabulary, one-word vocabulary." Tr. at 113. A.A. sometimes used gestures to communicate, such as pointing, bouncing, or taking one by the hand. Tr. at 113, 123. However, Ms. Edick specifically recalled that she could say "the words that a child would have at that time" and "numbers and count a little bit." Tr. at 113. She estimated that A.A. knew "approximately 12 to 20 words at that time."[64] Tr. at 123. None of A.A.'s behaviors at that time concerned her. Tr. at 113, 115. "She enjoyed playing . . . peek-a-boo, playing so big. If you asked her how old she was, she would hold up her finger, one." Tr. at 113. She appeared to understand what was being said and "would look to you to interact and . . . play." Tr. at 113. Ms. Edick noted A.A.'s eye contact in the photo taken of her playing croquet in her yard—"she was laughing and smiling for the camera." Tr. at 114 (discussing Pet. Ex. 76).

On Halloween, Ms. Edick recalled speaking to her sister on the telephone and asking if A.A. was dressing up to go trick-or-treating. Tr. at 116. She replied that A.A. "hadn't been feeling well, she was running a fever and had been for a few days." Tr. at 116; *see also* Tr. at 123; Pet. Ex. 79 at 3. Her sister promised to "dress her up another day and . . . send pictures when she's feeling better." Tr. at 116.

On Veterans Day weekend, the Edicks visited petitioners at their home. Tr. at 116; *see also* Pet. Ex. 79 at 3. During that visit, she became "very concerned because . . . it was apparent that [A.A.] was showing signs of development[al] regression, which included . . . an absence of speech and communication . . . [and] eye contact. Tr. 116-

[64] This estimate contrasts with Mr. Allen's testimony that A.A. knew "well over 100 words" by her first birthday (Tr. at 70-72) and the earlier report that she spoke "her first word 'Quack' at 1 year and [spoke] a little more/using animal sounds at 15 months" (Pet. Ex. 5, p. 5). A.A.'s pediatrician assessed her as having one to three words at her one-year well child visit. Pet. Ex. 9, p. 10.

17; *see also* Tr. at 124; *see also* Pet. Ex. 79 at 3. Her behavior was noticeably changed.

> She tended to just want to [lie] on the floor, or if we tried to pick her up, she didn't want us to touch her or pick her up. She would just stare at her hand, stare at her bear, stare at the carpet and pick the threads in the carpet. And it was quite alarming to me.

Tr. at 117.

And when the families visited the National Zoo, "[s]he stayed in her stroller all day" and showed "no interest in anything at the zoo." Tr. at 117; *see also* Pet. Ex. 79 at 3. Ms. Edick remembered that A.A. "cried a lot, whimpered" – "it was a very difficult trip for her." Tr. at 117-18; *see also* Tr. at 128; Pet. Ex. 79 at 4. Following the visit, Ms. Edick "may have said something" about her concerns to A.A.'s parents, but she did recall talking to her own parents "because [she] was very concerned[,] especially since [A.A.] had show[n] typical development in September." Tr. at 119; *see also* Tr. at 124-25, 130-31; Pet. Ex. 79 at 4. She stated that what she saw "really affected" her because A.A.'s "behaviors were autistic-type behaviors on the spectrum, signs of it." Tr. at 119; *see also* Pet. Ex. 79 at 4. She was not certain, though, that A.A. actually had autism and hoped instead that the behaviors were due to an illness. Tr. at 127, 130.

In December, Ms. Edick asked her parents to observe A.A. during their Christmas visit and report back on her behaviors and whether she had improved. Tr. at 119; *see also* Tr. at 124-25, 130. When they returned home, they informed Ms. Edick that the signs she had observed were "still apparent." Tr. at 119. They also expressed that "they were extremely upset because [A.A.] was having constant tantrums . . . throwing herself back and hitting her head on the floor." Tr. at 119; *see also* Pet. Ex. 79 at 4. Because of her behaviors, they left without seeing her open any gifts. Tr. at 119. Ms. Edick stated that she spoke with her sister after the holidays and "asked her at different times to talk to their pediatrician, . . . or follow through with a specialist, an ear nose and throat person to see if there was anything wrong with [A.A.'s] hearing or behavior." Tr. at 126.

In April 2001, their families gathered together for Easter. At that time, A.A. "was walking again, but . . . still did not communicate through speech or many gestures." Tr. at 120; *see also* Tr. at 128. Ms. Edick also recalled that she "did not want to socially interact with her grandparents or anyone," or engage in any age-appropriate activities. Tr. at 120. Also of concern was her unresponsiveness "to her name or commands" in potentially dangerous situations. Tr. at 120; *see also* Pet. Ex. 79 at 5. She observed A.A. to "just run randomly" into the woods or a nearby yard and that she did "not respond to her name or commands." Tr. at 120; *see also* Pet. Ex. 79 at 5. According to Ms. Edick, this was different from her previous behavior. Previously A.A. "always responded and stayed around people"—[i]f you called her, she would come to you." Tr. at 120.

In the summer of 2001, the Edicks visited petitioners. During their stay, she noted that some of the abnormal behaviors were persisting—"she still did not communicate, she still was not talking," and she still did not "have a lot of eye contact." Tr. at 121; *see also* Pet. Ex. 79 at 5. She also remembered that A.A. "was having a lot of crying and tantrums[,] . . . did not want to keep her clothes on[,]" and appeared to be "experiencing some . . . sensory issues[.]" Tr. at 121-22.

Ms. Edick indicated that she was not surprised when A.A. was evaluated on the autism spectrum, as she eventually suspected—and suggested—that autism was a possibility. Tr. at 122, 133-34. By that point, petitioners also did not seem too surprised, either. Tr. at 133. Although it was "very devastating" to accept, they had been seeking answers for some time—"it was such a bad period of time for them." Tr. at 133.

V. Expert Qualifications.

Four physicians offered opinions on vaccine causation and other matters in dispute. All of the experts were well-qualified to offer opinions in this case. Petitioners' experts opined that A.A. had an underlying mitochondrial disorder that made her vulnerable to the inflammatory effects of the MMR vaccine she received at her 15-month well child visit. As a result of her vaccination, she experienced a rapid regression and ultimately developed "mitochondrial autism." Respondent's experts opined that A.A. did not have a mitochondrial abnormality or suffer a rapid regression. Instead, she exhibited signs of autism prior to vaccination and followed a typical course thereafter. In their view, the MMR vaccine did not aggravate an underlying condition or cause her to develop ASD.

A. Petitioners' Experts.

Petitioners presented testimony from two experts: Dr. Andrew W. Zimmerman, an expert in pediatric neurology, and Dr. Richard I. Kelley, an expert in metabolism. Both physicians were involved in A.A.'s treatment and were familiar with her general medical history and development; however, neither was a treater at the time of vaccination or a contemporaneous witness to the onset of her condition. As such, these particular treating physicians are no more knowledgeable about what actually transpired after the vaccination than any other physician who testified in this case.

1. Andrew W. Zimmerman, M.D.[65]

Doctor Zimmerman earned his medical degree from Columbia University. Tr. at 289. He completed a pediatric internship at the University of Michigan, and a neurology residency at Johns Hopkins Hospital. Tr. at 289-90. Following his residency, Dr.

[65] Doctor Zimmerman's CV was filed as Pet. Ex. 26, and his expert report was filed as Pet. Ex. 25.

Zimmerman worked for eight years[66] as a faculty member at the University of Connecticut. Tr. at 290. Thereafter, he went into private practice for 11 years and "then returned to [the] Kennedy Krieger Institute and Johns Hopkins in 1994 for the next 16 years." *Id*.

For the past several years, he has worked at Massachusetts General Hospital as director of clinical trials at the Lurie Center for Autism, where he conducts drug trials on children with autism. Tr. at 290. He also is an associate professor of neurology at the Harvard Medical School. *Id*. His academic responsibilities involve teaching medical students, residents, and fellows. Tr. at 291. He is board certified in pediatrics and pediatric neurology. *Id*. He has published over 70 peer-reviewed articles—many focused on autism. *Id*.; *see also* Pet. Ex. 26 at 16-22. Doctor Zimmerman works with various hospital committees in his capacity at the Lurie Center and serves as the scientific advisory chair on the board of directors of the Fetal Physiology Foundation. Tr. at 291; Pet. Ex. 26 at 3.

2. Richard I. Kelley, M.D., Ph.D.[67]

Doctor Kelly earned his medical degree and a Ph.D. in pathology/molecular biology from the University of Pennsylvania, where he participated in a combined Ph.D./M.D. program. Tr. at 135; Pet. Ex. 24 at 1. He completed a residency in pediatrics and a postdoctoral fellowship in medical genetics at The Children's Hospital of Philadelphia ["CHOP"], after which he spent approximately five years on the CHOP faculty in the departments of metabolism and genetics. Tr. at 135-36; Pet. Ex. 24 at 1. Subsequently, he joined the faculty of the department of pediatrics at Johns Hopkins University School of Medicine ["JHU"] and also became a staff physician at the Kennedy Krieger Institute ["KKI"]. *Id*. Both institutions are located in Baltimore, Maryland.

Doctor Kelley is currently a professor of pediatrics at JHU and director of the division of metabolism at KKI. Tr. at 136; Pet. Ex. 24 at 1. In addition to an active clinical practice, he oversees several KKI laboratories that conduct biochemical and genetic testing. Tr. at 136-37. He is also "the principal advisor for the neurology division" and a coordinator for the "neurogenetics division." Tr. at 137. His academic responsibilities include teaching medical residents, "mostly . . . on an individual basis," and performing "consultations . . . when a question falls into [his] areas of expertise." *Id*.

He is board certified in pediatrics, clinical genetics, biochemical genetics, and cytogenetics. Tr. at 138; Pet. Ex. 24 at 13. Doctor Kelley stated that he is regularly consulted as a mitochondrial expert both domestically and internationally. Tr. at 139-40. He is "the go-to person" for certain developmental diseases and has been consulted on

[66] Doctor Zimmerman testified that he was on the faculty for eight years; however, his resume indicated that it was between six and seven years (January 1977 to August 1983). Pet. Ex. 26 at 1-2.

[67] Doctor Kelley's CV was filed as Pet. Ex. 24, and his expert report was filed as Pet. Ex. 23.

a number of "puzzling case[s]" involving "Smith-Lemli-Opitz syndrome, Barth syndrome, mitochondrial disease, chondrodysplasia punctata, [and] Zellweger syndrome." *Id*.

His publications include more than 100 peer-reviewed scientific articles and 12 book chapters. Pet. Ex. 24 at 2-11. He has written about "a fairly broad spectrum of metabolic abnormalities that largely come from clinical practice." Tr. at 138. His work has "been largely with metabolic and so-called inborn errors of metabolism;" however, the focus of his research "basically depends on what comes up in the clinic or . . . our laboratory" at any given time. *Id*.

Doctor Kelley previously served on numerous committees and boards, including journal review boards. Pet. Ex. 24 at 13-14. However, he resigned or withdrew from them beginning around 2006, when demands on his time increased. Tr. at 141.

B. Respondent's Experts.

Respondent presented testimony from two experts: Dr. Max Wiznitzer, an expert in pediatric neurology and developmental disabilities, and Dr. Stephen Cederbaum, an expert in pediatrics, inborn errors of metabolism and mitochondrial disease, and genetics.

1. Max Wiznitzer, M.D.[68]

Doctor Wiznitzer earned his medical degree from Northwestern University, and completed a pediatrics residency at the Cincinnati Children's Hospital. Tr. at 476. He also completed fellowships in development disorders at the Cincinnati Center for Developmental Disorders and in child neurology at the University of Pennsylvania System and at the Children's Hospital in Philadelphia. *Id*. Additionally, he completed a National Institutes of Health National Research Service Award Fellowship in disorders of higher cortical function in children at the Albert Einstein College of Medicine in New York. *Id*.

Since 1986, Dr. Wiznitzer has been a full-time staff neurologist at Rainbow Babies and Children's Hospital in Cleveland, Ohio. Tr. at 477. In his capacity, Dr. Wiznitzer has treated "thousands of children and . . . adults" with autism. Tr. at 482. He has "an extremely busy clinical practice" that provides him the opportunity to "see patients four to five half-days a week." Tr. at 480. He routinely reads EEGs, assists the epilepsy team when a member is out of town, and works "at least eight weeks in the year on the inpatient medical service," where he is responsible for "any children admitted to the neurology service" and provides consults on any neurology questions. Tr. at 480-81.

Additionally, Dr. Wiznitzer is a professor of pediatrics and neurology and international health at Case Western Reserve University School of Medicine. Tr. at 477.

[68] Doctor Wiznitzer's CV was filed as Res. Ex. L, and his expert report was filed as Res. Ex. K.

He has conducted research in a variety of areas, with a special interest in autism, which he began studying in 1986. Tr. at 481. As a researcher, he has been involved in "two seminal studies looking at the differentiation between autism, kids with developmental language disorder, and children [with] mental retardation." *Id*. Most recently, he participated in a study with high-functioning autistic children that sought "to alter the[ir] developmental trajectory" through "a pharmacologic intervention." Tr. at 481-82.

Doctor Wiznitzer is board certified in pediatrics, neurodevelopmental disabilities, and neurology, with special qualification in child neurology. Tr. at 477. He has published 60 peer-reviewed articles, 11 book chapters, and numerous abstracts. Res. Ex. L at 13-23. He also writes questions for the neurodevelopmental disability board certification exam. Tr. at 483. Doctor Wiznitzer regularly lectures on autism spectrum disorders and developmental disabilities at national and international meetings. Tr. at 482. He is a member of numerous professional organizations, editorial boards, and advisory groups. Tr. at 477-80.

2. Stephen D. Cederbaum, M.D.[69]

Doctor Cederbaum earned his medical degree from New York University School of Medicine, and completed an internship and residency at Washington University School of Medicine in St. Louis. Tr. at 376. Subsequently he worked for the National Institutes of Health, fulfilling his military service obligation, where he conducted biochemical research. *Id*. He then returned to Washington University for training in medical genetics, after which he accepted a position at the University of California at Los Angeles ["UCLA"]. *Id*. At UCLA, Dr. Cederbaum taught medical students, cared for patients with genetic disorders (particularly those with inborn errors of metabolism), and conducted basic scientific research, with a focus on urea cycle disorders and inborn errors. Tr. at 377-78.

Doctor Cederbaum is board certified in clinical genetics and biochemical genetics. Tr. at 378. He has published 150 peer-reviewed articles and 80 to 90 chapters and other contributions. Tr. at 379. Although he has not published extensively in the field of mitochondrial disease, he considered himself a "pioneer" on the subject due to his publication of "one of the first cases of mitochondrial disorders" in the 1970s. *Id*. He also "was a pioneer in the area of pyruvate hydrogenase deficiency, developing the first dietary therapy for it." *Id*. He has also lectured on mitochondrial disease nationally and internationally. Tr. at 381.

He is currently a professor emeritus at UCLA, which has allowed him to continue many of his previous pursuits, but at a reduced level of responsibility. Tr. at 377. He remains current with developments, research, and literature in the field of inborn errors of metabolism, and is a reviewer for a variety of journals. Tr. at 377, 379-80. Doctor Cederbaum has received notable honors and awards and remains a member of several

[69] Doctor Cederbaum's CV was filed as Res. Ex. B, and his expert report was filed as Res. Ex. A.

professional societies, including the American College of Medical Genetics, of which he was a founding member. Tr. at 380.

Doctor Cederbaum also works as a medical monitor for the mitochondrial research program at Columbia University. Tr. at 380. He previously worked in that capacity for the University of Florida. *Id*. Doctor Cederbaum explained that a medical monitor acts as an unbiased evaluator when questions arise about the safety of participants involved in research studies. *Id*.

VI. Causation Evidence.

A. Medical Literature.

The volume of medical literature submitted into the record renders a separate summary of each article impractical. Although I read and considered every piece of medical literature in the record, only the articles addressed by the experts or that I relied upon in coming to my conclusion will be specifically referenced below.

B. Expert Opinion and Testimony.

1. Doctor Zimmerman.

In his expert report, submitted prior to hearing, Dr. Zimmerman recounted that A.A. "had normal development until 16 months when she regressed in language and social skills within 1 – 2 weeks following immunization with MMR vaccine." Pet. Ex. 25 at 1. Based on her history, his evaluation and testing, and her response to treatment, Dr. Zimmerman concluded that A.A. "had a disorder of mitochondrial metabolism associated with autistic regression." *Id.* at 2. The report, however, contained no statement addressing the role of the MMR vaccine in the development of this condition.

Doctor Zimmerman began his direct testimony at hearing with a review of A.A.'s medical history and his involvement in her treatment. He first saw A.A. at an initial evaluation on February 13, 2002, when she was 30 months of age. He recalled that she presented with "a history of autism following regression." Tr. at 292. Based on parental report, she regressed "one to two weeks following her MMR immunization" with a "los[s of] language and eye contact and social interaction." *Id*. He stated that her early development "appeared to be normal" from "all standpoints"—she "had met all her milestones." Tr. at 292-93. Because of her history and presentation, Dr. Zimmerman "initiated a workup of genetic and metabolic studies." *Id*. [70]

[70] In his evaluation, Dr. Zimmerman wrote that A.A. "presents an atypical history and appearance consistent with an encephalopathy and a pervasive developmental disorder (autism spectrum). A history of regressive encephalopathy suggests the need for genetic testing, chromosomes and DNA for fragile X and quantitative plasma amino acids and urine organic acids." Pet. Ex. 6, p. 24. He also "requested genetic testing to rule out Rett syndrome." *Id*.

In response to questioning on cross examination, Dr. Zimmerman stated that the history he gave of A.A.'s regression in language and social skills shortly after her MMR immunization was based entirely on statements from her parents. Tr. at 347-48. He also indicated that prior to her initial evaluation he had not reviewed any of her medical records, although he has since done so.[71] *Id.* When asked whether he found any indication in the medical records of developmental abnormalities or changed behavior within one to two weeks of her immunization, he stated "I don't believe so, no." Tr. at 348.

During his testimony, Dr. Zimmerman viewed and commented on several segments of home video taken on October 14, 2000, about nine days before A.A.'s immunization. Petitioners argued that the video provides a demonstrative baseline for her pre-vaccination behavior and developmental achievement. In the video, which was taken at petitioners' home, A.A. seemed "quite lively." Tr. at 294. She appeared to respond to her name and play appropriately with toys, and said "quack" when asked what noise a duck makes. Tr. at 294-95. When questioned about her age, she indicated with a raised finger that she was one year old. Doctor Zimmerman assessed this behavior as appropriate for A.A.'s age. Tr. at 295. He also observed that in an earlier frame she was "pointing with [her] index finger"—an "important prelinguistic gesture that children develop around one year of age[.]" Tr. at 295-96.

He further noted that A.A. was appropriately interactive with her parents. Tr. at 296. "She's smiling and responsive and looking at the camera. I think she's actually making eye contact with the person who's taking the film." Tr. at 297. As for her language development, she was "not forming words," but "making word sounds." Tr. at 297. This was not a point of concern, but instead, evidence that "she's developing language." Tr. at 297. For example, when she said "moo" in response to the question "What does a cow say?", she was not simply repeating a sound someone made to her, but responding to a question. Tr. at 298. "She's practicing to be two." Tr. at 298.

On cross examination, Dr. Zimmerman stated that a 15-month-old child would typically have three words with meaning. Tr. at 343. When asked whether he heard A.A. say any words in the above-described video clip, he stated: "I guess the 'quack,' and at one point she said 'moo.'" Tr. at 344. He also recalled her "babbling some word sounds," but no other specific words. *Id.* When pressed whether he believed "moo" and "quack" were words rather than sounds, he stated that "moo" was a word in this context because A.A.'s response "was prompted only by the question, not by the sound."[72] Tr. at 344.

[71] I directed Dr. Zimmerman to consider the initial audiological evaluation of A.A. from Blue Ridge Speech & Hearing, which states: "Speech and language landmarks were reported as age-appropriate to a point, said first word at one year, spoke a little more at 15 months, stopped speaking after having three ear infections in a row." Tr. at 368 (quoting Pet. Ex. 5, p. 5). I asked him whether he still would have attributed A.A.'s regression to her MMR vaccination had he seen that record or been provided that history by her parents. Tr. at 368. He responded: "I would have taken this into consideration, yes." *Id.*

[72] On redirect, Dr. Zimmerman confirmed that "moo" is a legitimate word. He stated that the 1983 edition of Webster's Dictionary "clearly says it's a verb, to make the characteristic sound of a cow. So, she had a

He was also questioned about his comment that A.A. appeared to be making eye contact with the person taking the video. Tr. at 344-45. When asked whether he could differentiate between her "interacting or making eye contact with the person," and her simply "looking at the camera," he conceded that he could not know what she was looking at. Tr. at 345.

In response to my questioning, Dr. Zimmerman confirmed that he saw A.A. pointing on the video, but that he did not see any evidence of her using words, "except [for] what we have said, the – saying 'moo' and 'quack'." Tr. at 358. As for her raising a finger to show her age, he agreed that the action was not an indication that she knew her numbers, but that she had been "keyed or trained or talked to about putting that finger up." Tr. at 358; *see also* Tr. at 683-84. He also indicated that her reported ability to name colors was probably overstated based on the level of development he saw on the video. Tr. at 358-59 (citing Pet. Ex. 6, p. 15 (reporting that prior to her regression "she knew her colors and was using words and was pointing")).[73] "It would be a little advanced, actually." Tr. at 359.

In a later segment of the video, A.A. demonstrated normal gross motor skills by running around the house. Tr. at 295. Doctor Zimmerman commented that "[s]he has quite a good running gait for a child of that age." Tr. at 298. He also noted that she stood "without difficulty" and was "quite independent." Tr. at 298. In another clip, she was seen actively exploring her surroundings, responding to the word "no", and feeding herself—behaviors he judged as age-appropriate. Tr. at 299. When the video concluded, Dr. Zimmerman stated that A.A. "appear[ed] normal in . . . all respects." Tr. at 299.

On redirect, Dr. Zimmerman was asked to elaborate on the development that he saw during the October 14 video which he considered to be normal. Tr. at 674. He stated that overall he "thought the language, the social interaction and her movements were normal. Her activities . . . were appropriate for age." Tr. at 674-75. It is unclear why he considered her language to be normal and age appropriate. He previously testified that a 15-month old child would have three words with meaning, but characterized A.A.'s speech, as seen in the video, as "babbling" and stated that she was not forming words. *See* Tr. at 297, 344.

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word." Tr. at 677; *see also* Tr. at 680 (recross). He emphasized that it is a "meaningful" word "which is recognized." Tr. at 677. I conclude that "moo" was not a word that A.A. used to communicate; rather, it was a response to "what does the cow say," just as holding up her index finger was a trained response to a question about her age.

[73] *See also* Tr. at 33 (Mr. Allen stating that A.A. "understood the colors" of the croquet balls when she played the game over the Labor Day holiday in September 2000). I have no difficulty accepting that she understood that the balls were of different colors, and that one particular colored ball was "hers," but that is a far cry from knowing colors and labeling items with their color when asked to do so—a more common meaning for "knowing her colors."

Doctor Zimmerman also was asked to specifically comment on what he considered to be developmentally normal in A.A.'s behavior at the pumpkin patch that same day. Tr. at 675. In response, he identified her interest in the pumpkins and her ability to stoop and recover when playing with them. *Id.* She had a good running gait and was stable when walking. *Id.* He noted "a lot of facial expression" and "some reciprocal interaction with her parents." *Id.* He further noted that he did not perceive any difference in her behavior at the pumpkin patch from the earlier scenes when she was alone with her parents at home. *Id.*

Doctor Zimmerman was asked to review the medical record of A.A.'s 15-month well child visit, which occurred on October 23, 2000.[74] Tr. at 300. He stated that the record reflected "normal" development on all measured criteria. Tr. at 301. It also indicated that she received three vaccinations on that occasion: "MMR number one, Hib booster, and Hep-B." Tr. at 301.

Petitioners played several segments of home video taken on October 29, 2000, six days after A.A.'s immunization. Petitioners argued that the video shows marked changes in A.A.'s behavior. The video captured various moments during the pre-Halloween party that took place outdoors in petitioners' neighborhood.

After viewing the video, Dr. Zimmerman observed that A.A. seemed "less lively," had "virtually no facial expression," and looked as though she did not "feel well." Tr. at 301; *see also* Tr. at 678 (redirect). He also noted that she did not look at the camera or interact with her parents. *Id.* And although she walked at times, it seemed "stilted." Tr. at. 301; *see also* Tr. at 682 (recross). During one clip, A.A. is seen walking with her parents but was "not showing much expression on her own and [didn't] seem to be [as] interested in things, as she was before." Tr. at 302; *see also* Tr. at 677-78 (redirect); 682 (recross). In response to my questioning, Dr. Zimmerman reiterated that he thought A.A.'s "motor activity was diminished" and that she had less facial emotion as compared to her behavior on October 14. Tr. at 684-85.

Doctor Zimmerman indicated that the behavioral changes seen in the video correlated with the parental report that A.A. changed "within one to two weeks of the MMR immunization." Tr. at 302-03.

I asked Dr. Zimmerman whether the October 23 well child record reflected symptoms of an illness or a cold. Tr. at 353-54. He responded that it noted ear tugging, nasal congestion for one week, and treatment with the antibiotic amoxicillin. Tr. at 354. He confirmed that treatment with amoxicillin was indicative of an ear infection. *Id.* I then recalled his statement that A.A. appeared ill in the October 29th video and asked whether her behavior could have been the result of the illness reflected in the medical record. *Id.* He stated that he "would expect if the amoxicillin were treating an ear infection, that she would have felt better by . . . six days later." *Id.* He agreed, however, that if the infection was viral rather than bacterial, she might have still felt ill. *Id.*

[74] Pet. Ex. 9, p. 9.

I also asked Dr. Zimmerman about differences between the videos with regard to environment. Tr. at 355. He noted that the first video was taken at home, while the second was shot "outside in a party atmosphere." *Id.* He acknowledged that "they [we]ren't directly comparable" and discussed the impact that environment can have on a child's behavior. Tr. at 355-56. For example, if she were really shy, she might not feel comfortable participating in the activities. He stated, though, that he "would have expected her to be more reactive to her parents . . . and have more expression." Tr. at 356. Overall, however, he did not think the environment was a factor. Tr. at 679 (redirect).

Petitioners showed home video taken on Christmas Day 2000. Doctor Zimmerman observed that "[t]his [was] two months later, the opening [of] presents, and she doesn't show, again, interaction with the parents or . . . the toys. Tr. at 303. She also was "not vocalizing like she was initially" and "show[ed] very little facial expression, if any[.]" Tr. at 303.

Doctor Zimmerman was then asked to opine on the significance of the behavioral changes seen in the videos. Specifically, were they due to a transitory illness or possibly the result of her vaccination? He stated that, in his view, the post-vaccination videos indicated that her changes were not due to a temporary sickness, because she would have improved by Christmas. Tr. at 303. Instead, "her condition five days after the doctor's visit appeared to persist . . . two months later." Tr. at 303-04.

On cross examination, Dr. Zimmerman was asked whether he had seen any video of A.A. taken during the two-month period between October 29th and December 25th, or reviewed any medical records from that same period. Tr. at 346. He stated that apart from petitioners' affidavits, he had not seen any contemporaneous evidence. Tr. at 346.

Doctor Zimmerman next discussed his initial evaluation of A.A. on February 13, 2002. *See* Pet. Ex. 6, p. 23. In his report he noted that "[s]he was fussy and showed many features of autism; she didn't engage or sustain eye contact; she had word sounds . . . and would seek her parents' attention at times[.]" Tr. at 304. She was reluctant to engage in "ball-play" and demonstrated "mild instability in her truncal gait." Tr. at 305. He stated that her history and physical presentation—specifically, her "lack of language [and] eye contact, and repetitive behaviors," as well as her lack of reciprocation—led him to conclude that she "had an autism spectrum disorder." Tr. at 305.

Following his diagnosis, he ordered genetic and metabolic testing in an effort to discover the cause of her condition. Tr. at 305. The genetic test results were normal; however, several lab studies "showed . . . differences in her amino acids and liver enzymes, such as AST [aspartate transaminase] and ALT [alanine transaminase] and CK [creatine kinase]." Tr. at 306.

On cross examination, Dr. Zimmerman was asked to elaborate on his statement in his initial evaluation that A.A. "presents an atypical history and appearance consistent with an encephalopathy and a pervasive developmental disorder, autism spectrum." Tr. at 348 (citing Pet. Ex. 6, p. 24). In response to questioning, he clarified that what he was "really saying" was that she had "atypical development." Tr. at 348. He stated that he was trying to express that "[r]egression is not typical development." Tr. at 348. He also found the "rapidity of her regression to be striking." Tr. at 349. It was "somewhat unusual" and not characteristic of those seen in the general autism spectrum disorder population. Tr. at 349.

I questioned Dr. Zimmerman regarding the asserted rapidity of A.A.'s regression. Specifically, I asked him to consider the time period between the October 14 (pre-vaccination) video and the December 25 (post-vaccination) video, without regard to the October 29 video, and state whether he would still consider the behavioral changes to be rapid. Tr. at 353. He responded: "Three months would not be rapid, no." Tr. at 353.

A.A. was next seen by Dr. Zimmerman on July 15, 2002. Doctor Zimmerman reviewed the follow-up note he wrote after that visit.[75] He stated that he "wanted to get further testing and recommended the organic acids" and other tests because he suspected "that she might have mitochondrial problems." Tr. at 306-07. The basis for this belief was A.A.'s "apparently rapid deterioration following her MMR vaccine"—a pattern he had seen in other children with mitochondrial problems. Tr. at 307. He stated that he has "seen about 20 [children] over the years who have had this pattern and . . . then show up with elevated CK, AST, and alanine." Tr. at 307. He noted that "most" of the cases "were in conjunction with Dr. Kelley," but that he had "seen them separately from consultation with him." Tr. at 307. Doctor Zimmerman confirmed that he ordered additional testing, including "lactic acid, serum chemistries, liver functions, [and] CK – CPK [creatine phosphokinase]." Tr. at 308.

A neurology clinic follow-up note from A.A.'s next visit, on November 4, 2002, reflected the results of her laboratory testing.[76] Doctor Zimmerman recounted that "her lactate was slightly elevated, but CK was elevated, as was her AST." Tr. at 309. With regard to her elevated lactate, he explained that any struggling during the procedure would likely have affected the results.[77] In view of this, Dr. Zimmerman repeated some of the studies, the results of which were listed at the bottom of the record. Of particular interest were her elevated CK and AST levels. Tr. at 309. These outcomes led Dr. Zimmerman to assume that A.A. "might have mitochondrial dysfunction" and to "start[] her on levocarnitine [L-carnitine] or Carnitor." Tr. at 310.

[75] Pet. Ex. 6, p. 21.

[76] Pet. Ex. 6, p. 19.

[77] He also stated that "her potassium [was] also slightly elevated, which could be for a number of reasons, but it [struggling] could have also played into that." Tr. at 309.

On cross examination, Dr. Zimmerman explained that he did not order a repeat test of A.A.'s plasma lactate because lactate testing is often unreliable as a measure. Tr. at 350. He stated that "unless you're there when the lactate is drawn and know . . . exactly how it was drawn, it's hard to say if it's normal or not." Tr. at 350. As a result, he "usually [doesn't] rely on lactates very much[.]" Tr. at 350.

Doctor Zimmerman elaborated that he had seen the elevated biochemistries—specifically, the elevated CK and AST—in other patients with symptoms similar to A.A.'s and suspected that she had mitochondrial dysfunction.[78] Tr. at 310. In the past he had seen approximately 10 to 12 patients with such profiles and treated many of them "in a similar fashion." Tr. at 311. That is, he "start[ed] with carnitine, then [obtained] further studies, and then [progressed to] using a more complete mitochondrial cocktail of vitamins." Tr. at 311. Doctor Zimmerman stated that most of the patients, "in various degrees," had a positive response to the treatment. Tr. at 311.

When Dr. Zimmerman next saw A.A., it was at an unscheduled urgent visit on January 22, 2003.[79] Tr. at 312. He recalled that "she had had four generalized tonic-clonic seizures over the . . . previous several weeks, since starting on the carnitine." Tr. at 312. He suspected that "the seizures were stimulated by the carnitine, but [also] assumed that she probably had an underlying predisposition to have seizures because of autism." Tr. at 312. Doctor Zimmerman asked A.A.'s parents "to discontinue the carnitine" and bring her in for a visit. Tr. at 312. His plan following examination was to start A.A. on Depakote and order a repeat EEG after six weeks. Pet. Ex. 6, p. 15. He also made a referral to Dr. Kelley "for further evaluation of a metabolic disorder. Tr. at 313.

A.A. returned for a follow-up with Dr. Zimmerman on March 3, 2003, at which time she appeared to be doing well.[80] Tr. at 313. Although the Depakote "seemed to induce irritability," she had only one additional seizure, which occurred after "she had been sleep-deprived." Tr. at 314. As for her biochemistries, she had "elevated alanine to lysine ratio on an earlier study, normal on repeat; AST and CK were both elevated on two occasions; and the genetic testing was normal." Tr. at 314. At this time, A.A. had not yet seen Dr. Kelley, so Dr. Zimmerman discussed her case with him and asked that he see her earlier due to his "concern about mitochondrial dysfunction." Tr. at 314.

On April 8, 2003, Dr. Kelley saw A.A. for an initial consultation at his metabolism clinic. Doctor Zimmerman was asked to review Dr. Kelley's consultation report.[81] In response to questioning, Dr. Zimmerman stated that the report showed Dr. Kelley

[78] Doctor Zimmerman stated that he was referring particularly to the child discussed in the Poling article. *See* Poling, Pet. Ex. 25A.

[79] Pet. Ex. 6, p. 15.

[80] Pet. Ex. 6, p. 13.

[81] Pet. Ex. 6, pp. 3-7.

"found that [A.A.] had mitochondrial involvement and recommended . . . treatment with a vitamin regimen"—a "mitochondrial cocktail."[82] Tr. at 315. She was also restarted on Carnitor (L-carnitine), but at a lower dosage. Tr. at 315. Doctor Zimmerman explained that L-carnitine "increases Complex I activity" and the various other vitamins "increase[] electron transport chain activity." Tr. at 315.

In response to questions regarding the cocktail, Dr. Zimmerman stated that he has ordered the mitochondrial cocktail in his practice with the expectation that he would "see considerable improvement in the . . . child's functioning." Tr. at 317. He would specifically watch for "[i]mproved developmental milestones and activity." He recalled that he was "concerned about the carnitine" in A.A.'s particular case, "but starting her back . . . did not seem to cause problems[;] . . . she responded rather well." Tr. at 317.

A.A. returned for a follow-up with Dr. Zimmerman on July 14, 2003, a few days shy of her fourth birthday.[83] He characterized her as "doing remarkably well." Tr. at 318. He recalled that she had "responded to the cocktail, the parents were pleased, and she was sustaining eye contact; was more interactive, though briefly; seemed to play with imagination . . . ; and was using single words, word combination[s]. Tr. at 318; *see also* Tr. at 373-74 (redirect). She also had improved sleep. Tr. at 318. With regard to her seizures, he noted that he "had switched her medication from Depakote to Tegretol based on the fact that Depakote seemed to be activating her in a negative way, and I felt she would respond better to Tegretol at that point, since her seizures were controlled." Tr. at 318.

In response to my questioning, Dr. Zimmerman explained that Depakote and Tegretol both have side effects, which vary by individual; however, based on his own experience, Depakote seems to cause "activation"—screaming, irritability. Tr. at 359. Tegretol, on the other hand, "will often have a calming effect on adverse behaviors." Tr. at 360. Doctor Zimmerman stated that in A.A.'s case he "assume[d the improvement] was due to the Tegretol or at least withdrawing . . . the Depakote." Tr. at 360.

Doctor Zimmerman stated that he continued to evaluate A.A. and that she progressively "improve[d] over the years." Tr. at 319. In his opinion, her positive response to the vitamin cocktail was "an indication" that A.A. "more likely than not" had "an underlying mitochondrial dysfunction." Tr. at 319. With regard to her seizures, the medication was effective in preventing any further occurrences, and after two years A.A. discontinued the anti-seizure treatment without recurrence. Tr. at 319-20.

In response to my questioning, Dr. Zimmerman stated that his experience and expectations with regard to the effects of vitamin cocktails were personal and anecdotal. Tr. at 356. He was not aware of any studies that have systematically looked at whether

[82] The vitamin cocktail was composed of coenzyme Q10, vitamin E, vitamin C, thiamine, and lipoic acid. Pet. Ex. 6, p 7.

[83] Pet. Ex. 6, p. 1.

vitamin cocktails are an effective treatment for children with autism. Tr. at 356. He also acknowledged that most children with ASD diagnoses make some improvements over time, especially with proven therapies, such as speech therapy and ABA therapy, both of which A.A. received. Tr. at 356-57.

At this juncture, Dr. Zimmerman's testimony shifted to a discussion of his research and the connections he and others have made between mitochondrial dysfunction and autism.[84] Tr. at 320. Although he spoke knowledgeably in both these areas, he was unable to set forth a theory connecting vaccines to either mitochondrial dysfunction or autism. Indeed, he testified that he could not directly attribute autistic regression to the MMR immunization or any resulting inflammation. Tr. at 367.

His early research "revolved around neuroinflammation and microglial activation and basically immune studies in autism, looking for factors in the immune system that might be involved in . . . autism." Tr. at 320. He stated that there is indication that inflammation plays a role in the "autism process," but the work in this area has produced few definitive answers. Tr. at 320. It cannot be said "that in any one individual . . . inflammation is the cause of autism."[85] Tr. at 321.

Regarding mitochondrial dysfunction as a cause of autism, Dr. Zimmerman stated that he had "always considered [it a] possibility," but that it was not until he "went to Kennedy Krieger" and began working with Dr. Kelley that his interest solidified. Tr. at 321. He explained that "mitochondria have always been considered an important part of neurological disorders," but unlike "known" mitochondrial diseases, such as "Kearns-Sayre syndrome or MERRF [86] or MNGIE," [87] which are degenerative conditions, mitochondrial involvement in autism appears to impact development. Tr. at 321-22. He continued:

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[84] On cross examination, Dr. Zimmerman clarified that he is not a geneticist, metabolic specialist, or expert in mitochondrial disease. Tr. at 343.

[85] In response to my questioning, Dr. Zimmerman confirmed his opinion that inflammation is thought to play a role in autism, but cannot be said to be its cause in any one individual. Tr. at 360. He explained that his assertion was based on the findings of "microglial activation in all the postmortem samples" regardless of whether there was regression. Tr. at 360. Doctor Zimmerman was the coauthor of two papers on this topic: D. Vargas, et al., *Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism*, ANNALS NEUROL. 57(1): 67-81 (2005); D. Vargas, et al., *Immunity, neuroglia and neuroinflammation in autism*, INT'L REV. PSYCHIAT. 17(6): 485-95 (2005). Although these papers were not filed in this case, they were extensively discussed in the OAP test cases. *See, e.g.*, *Snyder*. 2009 WL 332044, at *88. In summary, the papers demonstrated microglial activation, but indicated that it might be the result of ASD, not the cause.

[86] MERRF (myoclonic epilepsy with ragged-red fibers) syndrome is "a familial type of mitochondrial encephalopathy of maternal (mitochondrial) inheritance, characterized by myoclonic epilepsy and mitochondrial myopathy with ragged red fibers." The syndrome "is usually caused by mutation within the mitochondrial gene encoding the tRNA specific for lysine." DORLAND'S at 1838.

[87] MNGIE (mitochondrial neurogastrointestinal encephalopathy) is one of numerous encephalopathies associated with mitochondrial abnormalities. DORLAND'S at 615.

> [ASD] is not a degenerative disease in the vast majority of patients. It is not something that gets worse with age, although some patients don't progress. If they regress, [it] occurs before the age of three, and [is] usually associated with this window of vulnerability[.] . . . [R]egressions typically occur between 15 and 24 months of age when there are profound changes in synaptic development taking place in the developing brain.

Tr. at 322.

He stated that researchers are coming to understand that "autism is a problem at the synaptic level." Tr. at 323. Although a number of brain regions are involved in autism, "the real problem is at the level of the connections, at the synapses," which are ever-changing during development. Tr. at 323. He explained that unregulated synaptic pruning during the early stages of brain growth is a likely cause of the regressions seen in some individuals during this period. Tr. at 322. The research in this area is unclear, though, as to "whether it's too much or too little" pruning, or something else that has "go[ne] awry." Tr. at 322. Some researchers theorize an acceleration or "exaggeration" of the normal pruning process due to "inflammation, probably from many different causes." Tr. at 323. He noted that "relatively few" causes of regression are known, but that "it is likely from a biologic standpoint that this is when and where the regression takes place in the brain." Tr. at 323; *see also* Tr. at 363-67 (court examination).

Doctor Zimmerman also discussed several research articles pertaining to mitochondrial dysfunction and autism. He stated that the articles, which were "primarily studies [of the] postmortem brain [tissue] of people with autism at different ages, demonstrate[d] differences in the autis[tic] brain with respect to mitochondrial function . . . , DNA mutations, and content of mitochondrial activity in different areas[.]" Tr. at 324.

In the first study, researchers compared the levels and activities of various mitochondrial proteins in the lateral temporal lobe[88] of autistic individuals and controls between two and 67 years of age. G. Tang, et al., *Mitochondrial abnormalities in temporal lobe of autistic brain*, NEUROBIOLOGY OF DISEASE, 54: 349-61 (2013), filed as Pet. Ex. 65 [hereinafter "Tang, Pet. Ex. 65"]. The researchers confirmed previous findings of "decrease[ed] protein expression and Complex I and IV enzyme activities in the temporal cortex" of ASD patients. *Id*. at 350. Additionally, they found "decreased protein levels of the mitochondrial antioxidant enzyme SOD2 and increased oxidative mtDNA damage in ASD patients aged 2-9 years." *Id*. Other differences in the ASD brain included altered mitochondrial dynamics due to an imbalance between fission and fusion proteins, and increased mitochondrial mass due to increased levels of mitochondrial membrane proteins. *Id*. The authors noted that "[m]any of these changes were evident in cortical pyramidal neurons, and were observed in ASD children but were less pronounced or absent in adult patients." *Id*. at 349. The authors concluded

[88] The lateral temporal lobe is "involved in auditory processing [and] language and social perception," areas "implicated in ASD-associated behaviors." Tang, Pet. Ex. 65, at 350; *see also* Tr. at 329.

that the study provided "evidence that mitochondrial function and intracellular redox status are compromised in pyramidal neurons in ASD brain and that mitochondrial dysfunction occurs during early childhood when ASD symptoms appear." *Id*.

In a second study, researchers compared the protein levels of various mitochondrial respiratory electron transport chain ("ETC") complexes in different brain regions from individuals with autism and age-matched controls. A. Chauhan, et al., *Brain region-specific deficit in mitochondrial electron transport chain complexes in children with autism*, J. NEUROCHEM., 117: 209-20 (2011), filed as Pet. Ex. 69 [hereinafter "Chauhan, Pet. Ex. 69"].[89] The researchers found that "children with autism showed a decrease in protein levels of ETC complexes in the cerebellum and the frontal and temporal cortices," but no differences "in the occipital and parietal cortices." *Id*. at 210. The researchers noted with interest that when the data was analyzed "as a function of age, children with autism (4-10 years of age) but not adults with autism (14-39 years of age) showed lower protein levels of brain ETC complexes[.]" *Id.* This suggested "that developmental mitochondrial abnormalities resulting in mitochondrial dysfunction, oxidative stress, and abnormal energy metabolism may contribute to [the] autistic phenotype." *Id*.

In response to questioning, Dr. Zimmerman stated that the "most important finding" in these two studies was the "clear difference between younger and older brains with respect to mitochondrial function." Tr. at 324. He stated that the researchers' findings mirrored his own experience with regard to the changes seen in certain clinical and laboratory measures as children age. *Id.* "I don't find them after they're . . . school-age, after five to ten." Tr. at 324. Indeed, if he tested A.A. today, he would expect her results to be different from those obtained years earlier. Tr. at 325. On this last point, Dr. Zimmerman was asked on cross examination whether he "believe[d] she has a disorder of mitochondrial metabolism anymore." Tr. at 351. He stated, "if she does, it's going to be difficult to find it." Tr. at 351.

Doctor Zimmerman viewed these differences as indicative of "a developmental process" that is "probably genetically regulated." Tr. at 325; *see also* Tr. at 363-67 (court examination). He explained that mitochondrial abnormalities are "more pronounced at the younger ages" due to "differences in gene expression" during different stages of development. Tr. at 326. "The genes that we inherit may be the same, but the way they're expressed . . . varies from one month or year to the next[]"—"allow[ing] for growth and development." Tr. at 326. This dynamic biochemical environment has made it difficult, however, to "nail down" the causes of autism, with many remaining elusive. Tr. at 326. He endorsed the idea that a child's particular autistic symptoms are determined by the state of his or her brain at the time an "insult occurs." Tr. at 327. This is why "there's so much heterogeneity . . . [in] children with autism"—"virtually no two children are the same who have that diagnosis." Tr. at 327.

[89] The study was "the first to report on brain mitochondrial abnormalities in autism." Chauhan, Pet. Ex. 69 at 216.

Doctor Zimmerman specifically referenced several portions of the Tang article he thought were noteworthy, including the researchers' confirmation of earlier findings by Chauhan that ETC abnormalities were more severe in ASD children than adult patients. Tr. at 327 (citing Tang, Pet. Ex. 65, at 357-58). Also significant was Tang's speculation that ETC abnormalities "may be secondary to environmental stressors, including aberrant calcium signaling, alterations in immune functions,[toxic compounds], or oxidative stress." Tr. at 332 (citing Tang, Pet. Ex. 65 at 358 (citing S.J. James, et al., *Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism*, FASEB J., 23:2374-83 (2009))).

When asked to elaborate on what the researchers' statements indicated regarding potential causes of autism, Dr. Zimmerman stated:

> Well, it's a – it means that the – the mitochondrial dysfunction may be an important underlying factor when other stresses take place. Inflammation, we know that autism can occur after or with certain infections. We know, at least in some cases, that it may be associated with immunizations. Anything that causes stress for the – on the mitochondrial system, and if the – if mitochondrial activity is less than sufficient to support synaptic function when it occurs, it – the – the added stress of the environmental stressor, as they describe it here, could be a variety of things.
> . . .
> That added stress, combined with a deficient mitochondrial activity, embarrasses the – the cells, and many of them shut down and causes continuing dysfunction.

Tr. at 332-33.

Doctor Zimmerman also expressed familiarity with the work of Dr. Jill James, whose 2009 research was cited by Tang. Tr. at 333. In response to questioning, Dr. Zimmerman briefly discussed James's work as it related to the Tang article. *Id.* He stated that "her work on oxidative stress . . . demonstrated that there's increased oxidative stress in autism for a number of reasons, including abnormalities in glutathione and other factors. So, it's an indication of mitochondrial dysfunction." Tr. at 333. According to Dr. Zimmerman, glutathione is an important compound regulating mitochondrial function. Tr. at 334. It is an antioxidant that "scavenges oxidative stress radicals," which "damage membranes." *Id.* He stated that the vitamin cocktail that he prescribes to patients with mitochondrial problems is designed to reduce oxidative stress. *Id.* He further stated that his and Dr. James's work could be considered mutually supportive. Tr. at 335.

With regard to the Chauhan article, Dr. Zimmerman briefly noted the studies' findings that young children with autism had "[l]ower levels of Complexes III and V in the cerebellum; Complex I in the frontal cortex; and Complex II, III, and V in the temporal cortex" as compared to older children and adults with autism. Tr. at 340 (citing Chauhan, Pet. Ex. 69 at 211-12). These findings were significant to Dr. Zimmerman

because they were "consistent with [his] findings clinically that . . . differences are more apparent in young children compared to older children and adults." Tr. at 341.

In a third article discussed by Dr. Zimmerman, researchers studied the "expression of 84 genes related to diverse functions of mitochondria, including biogenesis, transport, translocation and apoptosis" in the postmortem brain tissues of autism patients and controls. A. Anitha, et al., *Brain region-specific altered expression and association of mitochondria-related genes in autism*, MOLECULAR AUTISM, 3:1-12 (2012), filed as Pet. Ex. 66 [hereinafter "Anitha, Pet. Ex. 66"], at 1. They also studied the associations of certain genes with autism. The researchers examined brain tissues from the anterior cingulate gyrus, motor cortex, and thalamus, and found that "[s]everal genes showed brain region-specific expression alterations in autism patients compared to controls." *Id*. at 1. For example, some genes showed "consistently reduced expression" in autism patients. *Id*. Other genes showed an association with autism in some samples. *Id*. The researchers concluded that the "[d]ysfunction of these genes could lead to defects in mitochondrial activities, including energy metabolism, thus augmenting and disseminating several brain abnormalities related to autism. *Id*. at 10. Significantly, they conceded that it was not clear if mitochondrial dysfunction "is the cause or effect of autism," noting that "ASD patients have often been found to manifest biochemical or neuropathological traits linked with altered mitochondrial function." *Id*. at 9.

In response to questioning, Dr. Zimmerman explained that the brain regions examined by the researchers—the anterior cingulate gyrus, motor cortex, and thalamus—are thought to be areas from which autistic symptoms can arise. Tr. at 335-36. He stated that the cingulate gyrus is "an important area, because it integrates social and language and frontal lobe activity, and it's very much affected in autism." Tr. at 335. He also noted that it was one of the areas he "studied extensively" in his work on microglial activation. Tr. at 335. The motor cortex, on the other hand, "is generally unaffected in autism compared to other areas." Tr. at 335. Finally, the thalamus "is an important sensory way station" that "integrates sensory inputs and sends fibers out to different areas of the brain." Tr. at 335-36. He cautioned, however, that linking the sensory issues seen in autism "directly to the thalamus" would be incorrect—"they're probably widespread in the brain." Tr. at 336.

The study was noteworthy to Dr. Zimmerman because it showed differences in gene expression in the studied regions of the brain. Tr. at 336. The findings were important because abnormal gene expression results in changes—increases or decreases—in the production of proteins critical to proper cell function and energy metabolism, which is especially crucial during early development when the brain is growing and making connections. Tr. at 336-38. For example, "in the temporal lobe, if your mitochondrial function is decreased at a critical age," the cells in that area will be less able to respond "when an insult occurs." Tr. at 338. He emphasized that the temporal lobe is very sensitive to insults, especially in the context of mitochondrial dysfunction. Tr. at 338.

The final article discussed by Dr. Zimmerman studied gene dysregulation in autism. M.R. Ginsberg, et al., *Brain Transcriptional and Epigenetic Associations with Autism*, PLOS ONE, 7(9):e44736 (2012), filed as Pet. Ex. 67 [hereinafter "Ginsberg, Pet. Ex. 67"]. The researchers analyzed cerebellar and occipital brain tissues from idiopathic autistic patients and controls. *Id*. at 1. They identified "[n]o changes in DNA methylation . . . in autistic brain but [found] gene expression abnormalities in two areas of metabolism [.]" *Id*. Specifically, the researchers found "down-regulation of genes of mitochondrial oxidative phosphorylation and of protein translation[,]" as well as "associations between specific behavioral domains of autism and specific brain gene expression modules related to myelin/myelination, inflammation/immune response and purinergic signaling." *Id*. According to the researchers, their work highlighted "two largely unrecognized molecular pathophysiological themes in autism and suggest[ed] differing molecular bases for autism behavioral endophenotypes." *Id*.

Doctor Zimmerman had little to say about this article; however, in response to questioning he attempted to explain its significance. He stated:

> The important thing here is that they find differences in genes that don't – they don't find the differences in the occipital brain tissue . . . compared to the cerebellum. The cerebellum is another area of involvement in autism, whereas we look at the occipital region of the brain as being relatively uninvolved, unaffected.

Tr. at 338-39. He emphasized that this study supported an earlier point he had made: that the brain is not uniformly affected by autism—that "[d]ifferent regions of the brain can be differentially affected." Tr. at 339.

2. Doctor Kelley.

Of the four experts that testified, Dr. Kelley's testimony was the most challenging and least persuasive. The challenge came not from the difficult subject matter, but from Dr. Kelley's inability to clearly explain his methods and theories. As shown below, his testimony was littered with confusing tangents, unfocused narrative, and half-answered questions. His testimony was more poorly supported by published studies than that of the other witnesses, and in many cases the basis for his opinions were essentially "because I say so."

In his expert report, Dr. Kelley opined that A.A.'s history of acute regression, persisting neurological deficits, and biochemical abnormalities, were "compatible" with a "diagnosis of an inborn error[90] of mitochondrial energy metabolism"—specifically, a functional complex I deficiency. Pet. Ex. 23 at 2. Of particular significance to his opinion were test results obtained by Dr. Zimmerman, which showed "increased plasma levels of alanine and glycine, an increased AST to ALT ratio, a mildly increased creatine kinase level, electrolyte evidence of a metabolic acidosis, and a mildly increased blood

[90] He stated that the causative mutation had not been identified. Pet. Ex. 28 at 4.

lactate level."[91] *Id.* These results, together with A.A.'s history and clinical presentation, were "convincing" evidence of "a primary or secondary mitochondrial disorder."[92] *Id.*

Doctor Kelley elaborated that, in his experience "a combined increase in the plasma levels of alanine and glycine in a child with other clinical and biochemical signs of mitochondrial dysfunction and regressive autism always proves on muscle biopsy to be a deficiency of complex I or complex I + III." Pet. Ex. 23 at 2 (citing J. Weissman, et al., *Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis*, PLoS ONE, 3 (11): e3815 (2008), filed as Pet. Ex. 28 [hereinafter "Weissman, Pet. Ex. 28"]). Indeed, this finding is so consistent that he no longer orders "muscle biopsies for diagnosis of suspected mitochondrial disease." *Id.*; *see also* Tr. at 193; 275-78. Additionally, Dr. Kelley viewed A.A.'s positive response to treatment with L-carnitine[93] and other elements of the mitochondrial vitamin cocktail as supportive of the complex I diagnosis. *Id.* at 2, 4. He also stated that his analysis of A.A.'s amino acid profile showed her "profile [to be] the same as [that found] in most other children with regressive autism." *Id.* at 2 (citing Pet. Ex. 23A).

Doctor Kelley then offered his theory of "how a child with a mitochondrial disorder could be asymptomatic and developing normally for the first 15 months and then regress to a state of autism shortly after receiving an MMR vaccination." Pet. Ex. 23 at 2-3. He explained that his clinical work at the Kennedy Krieger Institute led him to the discovery of "mitochondrial autism."[94] *Id.* at 3. According to Dr. Kelley, children who have this "etiologically heterogeneous clinical disorder typically appear to be normal for their first 12 months or more before a viral illness or other stress[,] such as, rarely, an immunization, provides the critical metabolic stress that sufficiently compromises energy metabolism in the brain to precipitate acute or subacute cognitive and motor losses." *Id.*

[91] He noted that genetic testing was negative for identifiable genetic causes of autism spectrum disorder, including Fragile X testing, Rett syndrome mutation analysis, and urinary organic acid analysis. Pet. Ex. 23 at 2.

[92] At hearing, Dr. Kelley was asked to define primary and secondary mitochondrial disease. He stated that primary mitochondrial disease involves a "primary genetic defect in some component of the mitochondrion;" he did not clearly define secondary mitochondrial disease, implying that only deficits in mitochondrial DNA could be considered primary defects. Tr. at 182-83. However, authoritative research has shown that defects in nuclear DNA also cause mitochondrial problems. *See* R. Haas, et al., *The In-Depth Evaluation of Suspected Mitochondrial Disease: The Mitochondrial Medicine Society's Committee on Diagnosis*, MOL. GENET. METAB., 94 (1): 16-37 (2008), filed as Res. Ex. H [hereinafter "Haas, Res. Ex. H"], at 31) (stating that "[a]n estimated 75%-90% of pediatric primary mitochondrial disease results from nDNA mutations").

[93] He noted that A.A.'s initial negative response of "increased excitability and agitation immediately after starting carnitine" was not surprising, as "similar reactions occur in a subset of children with complex I deficiency and can be taken as supporting evidence for that diagnosis." *Id.* at 2.

[94] To aid in his explanation, Dr. Kelley appended a document entitled "Evaluation and Treatment of Patients with Autism and Mitochondrial Disease," which contained his unpublished research on this topic. *See* Pet. Ex. 23B.

He hypothesized that the injury likely occurs during this "window of vulnerability" because of an increase in glutamate-receptor density in the frontal cortex, "which is estimated to peak at 18 months." Pet. Ex. 23 at 3. According to Dr. Kelley, research has shown that increased glutamate-receptor density raises "the risk for excitotoxic neuronal damage." *Id.* He claimed that it is generally accepted that "any decrease in mitochondrial ATP synthesis capacity increases the sensitivity to glutamate excitotoxicity."[95] *Id.* (citing A. Novelli, et al., *Glutamate becomes neurotoxic via the* N-*methyl-D-aspartate receptor when intracellular energy levels are reduced*, BRAIN RES., 451: 205-12 (1988), filed as Pet. Ex. 41 [hereinafter "Henneberry,[96] Pet. Ex. 41]). As a consequence, children with "preexisting but otherwise asymptomatic mitochondrial dysfunction [are at] an increased risk of brain injury with chance occurrence of certain factors, such [as] mitochondria-impairing inflammatory stress, during the developmental stage of the frontal and prefrontal cortex"—the time frame "when glutamate NMDA [*N*-Methyl-D-aspartate][97] receptors are at their highest density." *Id.*

According to Dr. Kelley, "[a]n established principle of the pathophysiology of acute injury in many metabolic diseases, including mitochondrial disorders, is that the normal cytokine surges and catabolic stress of even simple viral infections can cause acute and sometimes fatal metabolic deterioration. Pet. Ex. 23 at 3. Of the "various cytokines released during an infection, tumor necrosis factor-alpha ["TNF-α"] is known to impair mitochondrial function as a normal part of the immune response that primes cells for mitochondria-mediated apoptotic death when infected." *Id.* He has found that the course of deterioration in most patients with regressive autism caused by complex I deficiency occurs "over days to weeks, often preceded in the parents' recollection by a viral illness, ear infection, or similar infectious process." *Id.* He noted, however, that in rare cases, "the regression follows within 48 hours of one or more immunizations, as illustrated by the now publicly known case of [child's first name] Poling."[98] *Id.* (citing Poling, Pet. Ex. 25A at 171). Doctor Kelley stated that the "most important fact linking [A.A.'s] deterioration to her MMR vaccination is that the peak level of TNF-alpha following immunization with the measles component of the MMR is between 10 and 15 days." *Id.* at 3 (citing I. Ovsyannikova, et al., *Cytokine production patterns and antibody*

[95] Excitotoxicity refers to the degree to which a given substance has a toxic excitatory effect on the nervous system. DORLAND'S at 653. An excitotoxin is any of a group of neurotoxic substances that are analogous to glutamic acid and mimic its excitatory effects on neurons of the central nervous system (e.g., *N*-Methyl-D-aspartate). *Id.*

[96] In his report and subsequent testimony, Dr. Kelley referred to this article by the name of one of its co-authors, R. Henneberry.

[97] *N*-Methyl-D-aspartate is a neurotransmitter similar to glutamate, found in the central nervous system. DORLAND'S at 1152.

[98] Doctor Kelley speculated that the regression the Poling child experienced within 48 hours was due to her receipt of "several killed-virus vaccines, which can induce immediate inflammatory responses because of previous immunizations with the same vaccines." Pet. Ex. 23 at 3. However, none of the listed vaccines in Poling, Pet. Ex. 25A, were killed virus vaccines. Either Dr. Kelley misspoke, or he was simply unaware of the nature of the relevant vaccines.

response to measles vaccine, VACCINE, 21: 3946-53 (2003), filed as Pet. Ex. 71 [hereinafter "Poland, [99] Pet. Ex. 71"]).

Doctor Kelley acknowledged the "absence of an association between the MMR vaccine and autism in large epidemiological studies." Pet. Ex. 23 at 3. He also stated that "autistic regressions caused by the live attenuated MMR vaccine are rare events." *Id.* However, in his view, the lack of statistical support between vaccines and autistic regression was not evidence against vaccine causation, but simply an indication that there are a "wide variety" of inflammatory factors that can precipitate a regression. *Id.*

In conclusion, Dr. Kelley reiterated his opinion that A.A. had "biochemical abnormalities diagnostic of an inborn error of mitochondrial metabolism, best characterized functionally as complex I deficiency, but with an as yet unidentified causative mutation." Pet. Ex. 23 at 4. He further opined, to a reasonable degree of medical certainty, that the "MMR vaccination administered 1 to 2 weeks before the onset of [A.A.'s] autistic regression at age 15 months was the direct precipitant of her neurological injury, leaving her with a diagnosis of autism with minor neuromotor abnormalities." *Id.* He emphasized, however, that A.A.'s "mitochondrial disorder is congenital and was not 'triggered' by the MMR vaccination. Rather, the MMR vaccination was simply one of several factors contributing to a typical inflammation-mediated metabolic injury." *Id.*

At hearing, Dr. Kelley testified consistent with his expert report. He began his testimony with a brief summary of A.A.'s reported medical history[100] and his involvement with her treatment. He recounted that by the time of his initial evaluation, Dr. Zimmerman had already commenced a partial workup, the results of which "raised the suspicion" of abnormal mitochondrial function. Tr. at 142-43. He noted that Dr. Zimmerman routinely screened his autistic patients for markers of mitochondrial function, as he was "aware of the association between mitochondrial abnormalities and autism." Tr. at 143. The screening involved an analysis of certain amino acid and enzyme levels known to be markers for mitochondrial function. Tr. at 142-4 3. The testing looked for disturbances in these markers. Tr. at 143.

As an overview, Dr. Kelley explained that mitochondria are double-membraned subcellular units that exist within nearly all cells of the body. Tr. at 145, 155. Their primary function is energy metabolism—they convert food into energy. Tr. at 145. This conversion is accomplished through a process called the citric acid cycle, also known as the "Krebs Cycle." Tr. at 146, 154; *see also* Trial Ex. 4. He stated that food molecules, such as fatty acids and glucose, are converted into acetyl-CoA, which is then combined with oxaloacetate to make citrate. Tr. at 148. Citrate is subsequently broken down in a

[99] The parties referred to this as the "Poland" article due to their hesitation at mispronouncing Dr. Ovsyannikova's name. Poland is the name of one of the other authors. To avoid confusion, I will cite to it as "Poland" as well.

[100] Doctor Kelley's summary did not differ in any important respect from that previously testified to by Mr. Allen, Ms. Edick, and Dr. Zimmerman, and will therefore not be detailed here.

series of steps wherein electrons and protons are extracted for addition to other molecules. Tr. at 148-49. In this pathway, variously known as the "electron transport chain" and "respiratory chain," electrons are combined with adenosine diphosphate ("ADP") to produce adenosine triphosphate ("ATP"), the basic energy currency of the cell. Tr. at 149-50. The process of transforming ADP to ATP is called oxidative phosphorylation, also known as "OXPHOS." Tr. at 154. Dr. Kelley explained that the electron transport chain consists of a series of five protein complexes,[101] each composed of numerous smaller protein subunits,[102] some of which are encoded by the mitochondrial genome, but mostly by the nuclear genome. Tr. at 149. He stated that "most mitochondrial disease . . . relates to dysfunction in the electron transport chain." Tr. at 149, 153.

In addition to fatty acids and glucose, proteins are also processed through the citric acid cycle. Tr. at 150. However, instead of generating acetyl-CoA, proteins are broken down into their component amino acids or converted into intermediates in the cycle. Tr. at 150. Doctor Kelley explained that abnormal levels of certain plasma amino acids can be an indicator of mitochondrial dysfunction, which is why amino acid testing, such as that performed by Dr. Zimmerman, is used for screening for mitochondrial disease. Tr. at 150.

Doctor Kelley discussed the significance of pyruvate, lactate, and alanine as indicators for metabolic functioning. Tr. at 155. Before entering the citric acid cycle, glucose must first be converted to pyruvate through a pathway known as glycolysis. Pyruvate is subsequently converted to acetyl-CoA or oxaloacetate for use in the citric acid cycle. Tr. at 148. Doctor Kelley explained that because of its role, pyruvate would be a valuable measure of mitochondrial function; unfortunately, it is a very unstable compound not easily or accurately measured.[103] Tr. at 155. Researchers have instead looked to lactate and alanine as proxies for pyruvate because they are in equilibrium. *Id.* However, because lactate is subject to artifacts in collection, "many people in the field have adopted using alanine as a proxy for pyruvate at the same time they measure lactate." Tr. at 155-56; *see also* Tr. at 169. Alanine is a stable amino acid in "very close equilibrium with pyruvate." Tr. at 155.

[101] The electron transport chain is composed of five complexes, designated with Roman numerals (I-V). Each complex has a defined role in the metabolism of food molecules and the production of ATP. The citric acid cycle is associated with Complex II. Tr. at 151-54.

[102] Doctor Kelley estimated that Complex I, for example, has more than 40 protein subunits. Tr. at 149.

[103] Doctor Kelley stated that pyruvate "is very, very difficult to measure except in a research laboratory." Tr. at 169. I note that I have frequently seen laboratory reports in Vaccine Act cases at least purporting to measure pyruvate or, more often, a pyruvate/lactate ratio, and that the ratio is commonly used as a diagnostic criterion in several of the most commonly used diagnostic systems. *See, e.g.*, E. Walker, et al., *Respiratory Chain Encephalopmyopathies: A Diagnostic Classification*, Eur. Neurol., 36: 260-67 (1996) at 262, filed as Res. Ex. T [hereinafter "Walker, Res. Ex. T"]; E. Morava, et al., *Mitochondrial disease criteria: Diagnostic applications in children*, Neurol., 67: 1823-26 (2006) at Table C,II, filed as Res. Ex. U [hereinafter "Morava, Res. Ex. U"]; F. Bernier, et al., *Diagnostic criteria for respiratory chain disorders in adults and children*, Neurology, 59: 1406-11 (2002) at 1409, filed as Res. Ex. V [hereinafter "Bernier, Res. Ex. V"].

Additionally, Dr. Kelley emphasized the importance of the amino acid proline, which "most biochemists know is a . . . marker for lactate." Tr. at 167; *see also* Tr. at 187-89 (direct); 665-68 (court examination). He analogized proline levels to the function of hemoglobin A_{1c} in measuring average blood glucose levels over time.[104] Tr. at 167, 188. He explained that similar to hemoglobin A_{1c}, proline levels, measured from a standardized collection, can show whether lactate was increased during a previous, albeit shorter, period.[105] Tr. at 168, 188.

According to Dr. Kelley, glycine is also an important indicator of mitochondrial function. Tr. at 169. Based on observation, he has learned that glycine levels are "virtually always increased" in patients who have a Complex I deficiency diagnosed with muscle biopsy. Tr. at 169. He attempted to explain; however, the result was less than clear:

> When I use the term [Complex I deficiency] clinically, I mean a relative impair – a relative block in the system at Complex I, which is where pyruvate is oxidized. So if you have anything that impairs Complex I, either a primary lesion in Complex I or a decrease in mitochondrial protein synthesis, because Complex I is a rate-limiting step, if one decreases the amount of mitochondrial protein overall, the first sign of a problem is a block at Complex I[.] . . . [A]lanine goes up and glycine goes up[.] . . . It's not entirely known why; it's more observational.
>
> But one of the main systems for metabolizing glycine directly connects with Complex I. So, the speculation is that [glycine] is high because it – you know, to get impairing pyruvate dehydrogenase's function impaired Complex I, impaired Complex I function impairs the glycine cleavage enzyme, as it's called.

Tr. at 169.

Doctor Kelley summarized that "the point [of] looking at the amino acids . . . is not so much to make a specific diagnosis, but to [ask] what's wrong with the mitochondrion?" Tr. at 157. He noted that not every mitochondrial disease disturbs citric acid cycle function, but most interfere in some way. Tr. at 157. Thus, "particular disturbances" in amino acid levels can provide insight into where the metabolic process is not working properly and enable treatment. Tr. at 157. Doctor Kelley indicated that it

[104] Hemoglobin A_{1c} is a glycosylated form of hemoglobin. Tr. at 187. It reflects mean levels of blood glucose over approximately the preceding three month period. Tr. at 188.

[105] In response to my questioning, Dr. Kelley stated that the length of the measurement is "not anywhere near as long as hemoglobin A_{1c} [, but] it's a surrogate for a phenomena that you would like to be able to measure on an hourly basis, but you can't." Tr. at 667.

was possible to determine where a block was occurring based on the amino acid profile and the given symptoms.[106] Tr. at 158.

Doctor Kelley then turned to A.A.'s amino acid profile, contained in Pet. Ex. 23A,[107] and his interpretation of the results. Tr. at 159. As a preface to the discussion, he stated that his method of analysis was "an elaboration on what many people do"—only taken "a couple steps further." Tr. at 159.

The profile was displayed in the form of a spreadsheet, with numerous columns and rows filled with data. The first column listed various amino acids of biological significance in the diagnosis of disease—30 in total. Tr. at 623. This was followed by a column of "range" values for each amino acid. Doctor Kelley stated that the ranges were found in a "paper from many years ago" where the authors "simply took a lot of amino acid samples from their clinical service, measured these ranges and published them in . . . a manual for metabolic diagnosis." [108] Tr. at 174; *see also* Tr. at 623; 628-29 (redirect); 662-65 (court examination).

The next column displayed "mean" values, which Dr. Kelley "determined and recalculated" using historical data from 100 samples he collected at his laboratory.[109] Tr. at 162, 176-77; *see also* Tr. at 624-25; 627-28 (redirect); 662-65 (court examination). He noted that the samples were all taken following a four-hour fast, the significance of which he discussed later in his testimony. Tr. at 161, 177; *see also* Tr. at 624-25 (redirect).

Adjacent to these initial columns were two columns of A.A.'s "amino acid data" obtained from testing performed on February 14, 2002, at KKI [the "KKI test"], and on

[106] As an example, Dr. Kelley discussed Barth syndrome, a genetic X-linked metabolic condition that causes boys to develop, among other things, cardiomyopathy. Tr. at 158; *see also* Tr. at 192. He stated that patients with this condition have extremely low levels of the amino acid arginine, which interferes with their ability to produce sufficient muscle protein. Tr. at 158. When he studied this disorder, Dr. Kelley hypothesized that a block existed at a certain enzyme; when he gave the children arginine, "it cure[d] the heart disease." Tr. at 159. "So that's . . . one of the more good examples of how one can look at the amino acids and learn a lot about mitochondrial function." Tr. at 159.

[107] Also filed as Trial Ex. 5.

[108] This paper was not submitted as an exhibit in this case. Doctor Kelley elaborated that he continues to use these traditional ranges because he is "not at the point yet of publishing" his own range values. Tr. at 175. He still needs to "go[] through all the documentation to say that . . . [his] new values are valid." *Id.* Doctor Kelley stated that the traditional ranges were not based on samples obtained after a four-hour fast. Tr. at 629.

[109] On cross examination, Dr. Kelley stated that the historical data he used was not publicly available for review or verification. Tr. at 654-55. He stated that all of the samples were collected from children with developmental problems; their diagnoses, however, were believed to have no effect on biochemistry. Tr. at 653-54. In response to another question, Dr. Kelley stated that he had not yet generated ranges for the mean values because he "wanted to get up to 200" samples; however he promised that "the data are there" and he could "fill them up on a spreadsheet now." Tr. at 655.

August 21, 2002, by Quest [the "Quest test"], an independent commercial laboratory.[110] Tr. at 161; *see also* Tr. at 631 (redirect). The numbers represented the raw data obtained from the testing. Tr. at 631. These columns were followed by a set of columns containing "ratios to mean" values for the amino acid data. Doctor Kelley explained that the ratio to mean for each result was calculated by dividing a given amino acid value by the corresponding mean value. Tr. at 162. For instance, the proline value from the KKI test was 137 and the related mean value was 161, so "137 divided by 161 is .85," which was the ratio to mean for that test result. Tr. at 162; *see also* Tr. at 632-35 (redirect).

The final set of columns contained "normalized ratios to mean"[111] values, which were a key component of his analysis. Unfortunately, Dr. Kelley had significant difficulty elucidating how these values were calculated. *See* Tr. at 159-60; 165-67; 635-45. He began that it is common practice to use the ratios of certain amino acids as supportive evidence of a mitochondrial diagnosis. Tr. at 159-60. As an example, he noted that increased pyruvate levels (or alanine as a proxy for pyruvate) relative to other "index" amino acids,[112] such as lysine or tyrosine, is suggestive of a mitochondrial problem.[113] Tr. at 159-60. His method of analysis, he explained, takes "that concept and expand[s] it to involve . . . other amino acids, because each amino acid has some flaw in being used as an index, alanine to lysine, alanine to tyrosine." Tr. at 160. He continued:

> Each of those ratios has some pitfalls. So, we average out the ratios by looking at the set of amino acids that have very few artifacts built into them or are subject to very few artifacts of collection or metabolism and just expand that ratio. And we simply index that to a value of one. So, we do a calculation to say that if everything were exactly as it should be, the ratio in this final column should be one and the – there are, I'd say, multiple pathways that are related to the mitochondrial function, which can throw these ratios off.

Tr. at 160; *see also* Tr. at 635-45 (redirect).

Doctor Kelley emphasized the importance of a four-hour fasting blood sample—"plus or minus"—to obtain accurate results. Tr. at 162, 164; *see also* Tr. at 626-27 (redirect). He explained that after a meal, "amino acid levels from protein go up and

[110] Doctor Kelley emphasized that although the results were obtained from different laboratories, "amino acid quantitation is quite standardized" and "very reproducible from laboratory to laboratory." Tr. at 161.

[111] Doctor Kelley stated that "normalized ratios" are ratios "divided by a number to bring them back to a certain standard." Tr. at 635.

[112] He indicated that the index amino acids are selected because they are known to be "largely unaffected by problems in the citric acid cycle or in mitochondrion, with some exceptions." Tr. at 159.

[113] According to Dr. Kelley, "it's stated, for example, in the literature that an alanine to lysine ratio greater than three is evidence of a mitochondrial problem, not diagnostic, but supportive evidence of that diagnosis." Tr. at 159-60.

they go up in an unpredictable way based on . . . what someone eats." Tr. at 163. When he orders biochemical testing, he instructs that the patient fast for between four and five hours. Tr. at 629. He has determined this time frame to be the "ideal range" because "everything's back to baseline" by that point—"all [of] the [amino acid] ratios are relatively constant." Tr. at 163-64; *see also* Tr. at 177-79 (direct); 630-31 (redirect). He stated that he did not know the exact amount of time A.A. fasted for the KKI test, but he could "tell that it was more than four hours" based on the lower-than-expected levels of certain amino acids. Tr. at 163; *see also* Tr. at 177-79 (direct). The Quest test, however, was performed "with very specific instructions to fast for four hours."[114] Tr. at 161; *see also* Tr. at 659 (cross).

Doctor Kelley explained that he drew the conclusion about the KKI test by comparing the amino acid values with the corresponding mean values.[115] He stated that the test values were lower than the mean values, which indicated to him that A.A. had fasted for more than four hours. Tr. at 164, 177-78. To illustrate his point, he directed attention to specific results on the spreadsheet. He began with glutamic acid; however, the KKI result was higher than the mean, while the Quest result was lower, which was opposite of what he wanted to show. Tr. at 164; *see* Pet. Ex. 23A. Doctor Kelley quickly moved on because "well, glutamic acid is not one of the ones that we used because it's subject to artifacts." Tr. at 164. He then pointed to the branched chain amino acids, "which are pretty reliable." Tr. at 164. The first result he noted was for valine. In this instance, the KKI value was lower than the mean, but so was the Quest value—indeed, the Quest value was not only lower than the mean; it was lower than the KKI value. Tr. at 164. Eventually, he found results (isoleucine and leucine) to support his point. Tr. at 164. "As I say, there's a lot of variation, minor variation." Tr. at 164-65.

Typical of his testimony as a whole, Dr. Kelley then launched into a meandering, confusing, and completely unpersuasive elaboration of his unique insights and methods. Tr. at 165-67. Immediately following the above-described explanation, he continued:

> But the – when you average everything up, they're – when you take an average of all these ratios – so, this is a – each one of these is a ratio to the mean. And for about 14 of these – of the amino acids that are not subject to or have few things that influence their level other than the time after a meal, which if you average all of those ratios, you find that the ratio for sample one at KKI was .9 – it got cut off. It's like .9 and the one here

[114] Doctor Kelley stated that he did not presume that his instructions were followed. Tr. at 659. He explained that the values themselves were indicative of a four hour fast—he knows the values that certain compounds should have at four hours fasting. Tr. at 660.

[115] On cross examination, Dr. Kelley was asked whether it was problematic to compare A.A.'s amino acid values, which were from a supposed non-fasting sample, against mean values generated from four-hour fasting samples. Tr. at 656-57. He replied that "generally" one would want to compare four-hour fasting samples to other four-hour fasting samples; however, his calculations bring everything "back to some standard." Tr. at 657. He understood how the concept "may be a little foreign" to those "not used to statistics." *Id.*

> was, I think, 1.05 or something like that. .9, the ratios are all less – means that the average ratio is less than one, which means that she's gone beyond the four-hour fasting point. The one that – from a physiologic standpoint. It could have been four hours fasting, but physiologically, she was beyond what we see in the average four-hour fasting sample. So, it's simply a way of being able to compare one amino acid sample to another one, in a standardized way if the – if the – too many amino acid ratios are too high or too many are too low, I, in effect, throw out the sample. I say I can't evaluate that. It has to be close to what we would predict for a four-hour fasting sample. This is – I think a lot of my colleagues recognize this is not standardized – or it's not a standard approach, but it is – I've been doing it for ten years or so and it's a – it just makes the interpretation so much simpler.[116]

Tr. at 165; *see also* Tr. at 635-45 (redirect).

Despite the unconventional nature of his method, Dr. Kelley was confident that the resulting data could be used "in a significant way for [A.A.] because we're very careful to standardize the conditions to produce the state where the amino acid levels in the blood reflect the physiology of the mitochondrion and other things." Tr. at 166. He explained that this provides a "stable basis for comparison" so that he can "go through the calculations." Tr. at 166-67. Doctor Kelley did not explicitly state what "the calculations" produced, but he seemed to be referring to the normalized ratios to mean values, which he indicated would all be "one" if he obtained "a perfectly normal sample of four hours fasting in the ideal child." Tr. at 166-67. In passing, he also mentioned that the range values for the normalized ratios to mean, noted on the spreadsheet as "0.8 to 1.2 (approx)," were based on 200 controls he had collected in his laboratory. Tr. at 167. Although the underlying data was not disclosed, Dr. Kelley assured that he has "the statistics [to] show that the normal range for most of these ratios is 0.8 to 1.2." Tr. at 167; *see also* Tr. at 181.

Doctor Kelley then discussed the specific test results in A.A.'s profile that he viewed as indicative of mitochondrial dysfunction—particularly those for glycine, alanine, and proline. Tr. at 168-70. However, rather than focusing on the actual test values, which were often within the expected range, he emphasized the normalized ratios to mean values that he derived using his unpublished methodology.[117] The actual values for glycine were normal for both tests (KKI and Quest), while the normalized

[116] Doctor Kelley stated that his approach was a "logical extension" of other established methodologies used to study metabolic disorders. Tr. at 647. He elaborated that his methods were "in effect, bringing amino acid analysis up to date. It's fallen far behind other methodologies in simply using normal ranges. And that's rather primitive in the analysis of amino acids because of the difficulty of obtaining samples on children." Tr. at 647.

[117] Doctor Kelley explained that he generally does not rely on the traditional range values in his analysis because they are established in "laboratories run by PhDs" who are not necessarily aware of physiology—"they're not clinicians." Tr. at 172.

ratios were both elevated.[118] Tr. at 170; Pet. Ex. 23A at 2. For alanine, the actual value was normal for the KKI test, but significantly elevated for the Quest test; however, both normalized ratios were elevated.[119] *Id.* Similarly, the actual value for proline was normal for the KKI test, but elevated for the Quest test. *Id.* When he "normalized" the ratios for proline, only the Quest test was elevated.[120] *Id.*

Doctor Kelley addressed these discordant results by reiterating the importance of collecting blood samples under standardized conditions—especially the four-hour fast protocol. Tr. at 170; *see also* Tr. at 644-46 (redirect). He attributed the apparently normal results for the KKI test to A.A. having fasted well beyond the ideal time frame, making it an unreliable measure of mitochondrial function. Tr. at 168-70, 186. In contrast, the Quest sample, which was collected under the stringent "ideal conditions" directed by Dr. Kelley, showed "high proline, which means high lactate, [and] a high glycine and a high alanine that imply Complex I deficiency." Tr. at 170. With that said, he still found the normalized ratios for the KKI test to be "convincing" given that the glycine and alanine values were 5.6 and 4.4 standard deviations above normal, respectively.[121] Tr. at 170. As a comparison, the normalized ratio for alanine from the Quest sample was "ten standard deviations above normal." Tr. at 167; *see also* Tr. at 181 (stating that the alanine value of 2.09 was "almost 11 standard deviations above normal").

According to Dr. Kelley, A.A.'s amino acid profile reflected the "classic pattern" of a child with Complex I deficiency and regressive autism. Tr. at 178. He elaborated that either sample was "very suspicious" because glycine and alanine increased together "almost always, at least 90 percent of the time, . . . comes back as a Complex I deficiency [on] a muscle biopsy."[122] Tr. at 178-79; *see also* Tr. at 193-94.

On cross examination, Dr. Kelley stated that he uses the term "Complex I deficiency" from a functional standpoint. Tr. at 237-38. He explained that "Complex I deficiencies for most people mean[] a specific deficiency of [the] Complex I subunit, for

[118] The actual test values for glycine: KKI (291); Quest (292); range (87-323). The normalized ratio values for glycine: KKI (1.56); Quest (1.35); range (0.8-1.2). Pet. Ex. 23A at 2.

[119] The actual test values for alanine: KKI (379); Quest (634); range (136-440). The normalized ratio values for alanine: KKI (1.44); Quest (2.09); range (0.8-1.2).

[120] The actual test values for proline: KKI (137); Quest (282); range (51-271). The normalized ratio values for proline: KKI (0.93); Quest (1.66); range (0.8-1.2).

[121] In response to questioning on cross examination, Dr. Kelley agreed that A.A.'s glycine levels on both tests were normal when evaluated against the traditional range values and became abnormal only when using his own ratios. Tr. at 239-40.

[122] On cross examination, Dr. Kelley confirmed that his opinion regarding A.A.'s complex I deficiency was based on the abnormalities seen in her profile, particularly the glycine and alanine values. Tr. at 238. He stated that the profile was "exactly what we see in an otherwise well-defined Complex I, based on standard criteria, muscle biopsy, or a molecular diagnosis." Tr. at 238.

example, or a muscle biopsy showing a deficiency in Complex I." Tr. at 238. He continued: "The studies I do show a pattern that correlates with those findings, even though I can't say and even though we know, theoretically, that abnormalities other than Complex I itself can cause that profile. So, I call it a Complex I profile." Tr. at 238.

In response to my questioning, Dr. Kelley stated that the normalized ratios to mean values for glycine and alanine on both tests were not necessarily diagnostic, but indicated a "very high likelihood" of Complex I deficiency.[123] Tr. at 180. Additionally, he stated that he would hold that opinion even if he had "just one sample" to evaluate. Tr. at 180. I noted that this was contrary to other diagnostic criteria for mitochondrial diseases, which typically require more than one laboratory sample.[124] Tr. at 180. Doctor Kelley responded that multiple samples are unnecessary if collection is standardized, because standardization eliminates the variability that necessitates numerous samples. Tr. at 180-81.

I questioned Dr. Kelley about the frequency of discordant results from testing, specifically, how often test results "would be suggestive, if not diagnostic, of a Complex I deficiency" from one lab and not another. Tr. at 181. In response he stated: "That will happen[, but] . . . when one looks at the mean levels, they're different – they're obtained at different physiological states. One's fasting, one's not fasting. I don't see a discrepancy if they're collected at the same point of fasting." Tr. at 181. He reiterated that it is "very uncommon" to "see discordant results if they're taken at the same level of fasting." Tr. at 182; *see also* Tr. at 184-85.

After listening to Dr. Kelley explain his method and interpret the results, I asked him how many other laboratories were using his system of analysis across the country. Tr. at 172. He stated that he did not know if any laboratories were using it, but stated that its "clinical utility" is "clear" to a number of clinicians.[125] Tr. at 173. He implied that the lack of adoption by laboratories was due to his not having "had time to publish it." Tr. at 173. He lamented that it "takes a long time" to generate the data necessary "to convince people." Tr. at 173. Later in his testimony, Dr. Kelley stated that clinicians become convinced once he describes his method and shows them that the values for "proline, alanine and glycine were not normal" compared to "the other amino acids." Tr. at 190. They ultimately find his method better "than the alanine-lysine ratio, which is

[123] Doctor Kelley later stated that taken together, the trio of normalized ratios to mean values for proline, glycine, and alanine from the Quest test were "in [his] view, diagnostic"—the "strength is in the numbers." Tr. at 187.

[124] *See, e.g.*, N. Wolf and J. Smeitink, *Mitochondrial disorders: A proposal for consensus diagnostic criteria in infants and children*, NEUROL., 59: 1402-05 (2002), filed as Court. Ex. 1 [hereinafter "Wolf and Smeitink, Court. Ex. 1"], at Suppl. Data (requiring at least three samples for evaluating lactate).

[125] On cross examination, Dr. Kelley was questioned about his method, particularly his use of normalized ratios. Tr. at 239. He confirmed that other laboratories have not adopted his method and that he has not published "how [he] got [the] ratios." Tr. at 240-41. He clarified, though, that certain individuals within laboratories have used the results of his analysis in their reports. Tr. at 240-41.

more traditional, but . . . has many pitfalls to it."[126] Tr. at 190. Indeed, "[o]ne could miss a mitochondrial diagnosis just using that ratio."[127] Tr. at 190.

Doctor Kelley discussed the treatment he ordered for A.A. based on her amino acid profile. Tr. at 194. He stated that the "first step" was to prescribe carnitine and "a standard combination of antioxidants." Tr. at 194-95; *see also* Tr. at 192-93. He explained that carnitine is a vitamin-like compound that can be used to activate Complex I through its interaction with acetyl-CoA, a compound "very central to energy and metabolism." Tr. at 195-96. He stated that for children like A.A., who are "right on the edge," carnitine can "activate Complex I and push [them] back [to stability]. [T]hat's the concept behind using carnitine." Tr. at 196-97.

In response to questioning, Dr. Kelley elaborated on the meaning of "on the edge." Tr. at 199-201. He stated that many children with mitochondrial disease or other metabolic abnormalities "can be perfectly healthy and normal until they hit some stress," which "puts a greater demand on the system" and they basically "fall apart." Tr. at 200. He explained that someone with normal Complex I activity can withstand a "certain degree of impairment without seeing change whatsoever." Tr. at 200. However, someone with lowered Complex I activity is "closer to the edge"—they are sensitive to additional stress. Tr. at 200. The idea is to increase Complex I activity to move them back from the edge. Tr. at 200. Although it "doesn't take away the disease entirely," it can provide them with some reserve to "withstand the daily stresses." Tr. at 200. He continued:

> So, again, . . . most children with regressive autism are . . . relatively normal developmentally up to a year, and then some of the children will develop regressive autism due to some stress – in the broadest sense of the term "stress" – that in turn with a mitochondrial disorder or with mitochondrial autism, as we call it, there are various stressors, usually an infection, that they know what infections do to the mitochondria in terms of lowering mitochondrial function and that is the added stress that can push them over the edge and do the damage.[128]

Tr. at 200-01.

[126] Doctor Kelley claimed that "[t]here's literature published that talks about the alanine-lysine ratio, which is the same concept, but expanded to get rid of a lot of the artifacts." Tr. at 190. He elaborated that "if someone understands amino acid physiology, this is not rocket science. This is very logical, very straightforward." Tr. at 191.

[127] Doctor Zimmerman considered this ratio in an early evaluation: "I note that she had normal quantitative amino acids, including the alanine/lysine ratio." Pet. Ex. 6, p. 21.

[128] In response to my questioning, Dr. Kelley acknowledged that regression can occur without any apparent stress. Tr. at 201. He stated, however, that some mitochondrial disorders were "much more susceptible to stress" than others. Tr. at 201.

With regard to the antioxidant component of A.A.'s treatment (*i.e.*, the "vitamin cocktail"), Dr. Kelley explained that a "common phenomenon" in mitochondrial disease is free radical damage. Tr. at 202. He stated that a free radical is "basically an electron gone wild," inflicting damage to the inner mitochondrial membrane. Tr. at 203. He stated that all mitochondria produce free radicals, but they also have a natural system for trapping and neutralizing them. Tr. at 203. However, with certain functional impairments, the system fails to work properly, resulting in increased free radicals. Tr. at 204. Antioxidants such as vitamin E, lipoic acid, and Coenzyme Q, can help "reverse" the damage done by free radicals. Tr. at 203-04. Doctor Kelley stated that "when the antioxidants are given, the abnormalities we measure in the citric acid cycle gradually go away, in addition to the change that occurred in Complex I with the carnitine." Tr. at 205. He recounted that in "some patients that we give carnitine, we see some improvement biochemically and clinically, and then we add antioxidants and we see further improvement. So, it's a two-step treatment." Tr. at 205. Doctor Kelley also noted that A.A. was given thiamine and vitamin B5. Tr. at 208. He explained that "a subset of patients with Complex I deficiency" respond to thiamine, although it is not clear why; and vitamin B5 is thought to enhance the action of carnitine. Tr. at 208.

I questioned Dr. Kelley regarding the efficacy of vitamin cocktails in light of the lack of evidence showing that such treatments result in clinical improvement. Tr. at 205. He responded that the reason most mitochondrial experts have not seen improvement is because their cocktail recipe is not properly balanced. Tr. at 207. He elaborated that "if you do vitamin E by itself, which some people do, it's toxic. If you give Co-Q by itself, it can be toxic. You have to have the complete system activated, and very few people do that." Tr. at 207.

As to whether the vitamin cocktail was beneficial to A.A., Dr. Kelley stated that he had "heard" she responded well, but conceded that he had not seen her for over 10 years, since 2002.[129] Tr. at 208-09. At the hearing, Dr. Kelley interacted with A.A. but found it difficult to assess her progress, since he would be comparing "a child who was just a few years old to someone her age now." Tr. at 208-09. He likened the comparison to "apples and oranges." Tr. at 209.

Doctor Kelley then returned to the subject of metabolic stress and how it could lead to an autistic regression in children with mitochondrial problems. In an unfocused narrative, he attempted to discuss some of the many different "mechanisms" of injury that can cause such deterioration. Tr. at 209-22. He eventually alighted on the theory presented in his expert report—that the inflammatory response produced by a stressor, such as an infection, a virus, or a vaccine, can cause neurological damage in children with impaired mitochondrial function. Tr. at 216-17. According to Dr. Kelley, there is a "window of vulnerability" between the ages of 12 and 24 months, when children like A.A.

[129] In response to my questioning, Dr. Kelley stated that he did not perform any post-treatment biochemical testing on A.A. to evaluate the cocktail's effectiveness, although he has done such testing on other children in the past. Tr. at 665.

are highly vulnerable to the effects of metabolic stressors.[130] Tr. at 213-14. This vulnerability is largely due to increased glutamate NMDA receptor density in the forebrain during this period of development.[131] Tr. at 214. He also briefly discussed the role cytokines in the inflammatory response—particularly, TNF-α, a cytokine that induces apoptosis, or cell death. Tr. at 216-22. Doctor Kelley stated that in his clinical experience, "if there is an identifiable event or identifiable time frame in which regression occurs, the factor that links it is inflammation." Tr. at 217. In A.A.'s case, he saw a "reasonable argument" for vaccine causation based on inflammation during the window of vulnerability. Tr. at 218; *see also* Tr. at 285-88 (redirect).

In response to questioning, Dr. Kelley indicated that inflammation from an infection was different from that generated by a vaccine—it had a different cytokine "profile." Tr. at 218-19. However, "correlations have not been made" regarding "what combination of cytokines [is] most likely to impair mitochondrial function." Tr. at 219.

Doctor Kelley stated that he recommends immunizations for children with mitochondrial disorders, unless extremely unstable. Tr. at 222-23; 651. However, as a precaution he "pre-treats" such children with the asthma drug Singulair," which "directly blocks the TNF-alpha system."[132] Tr. at 223; *see also* Tr. at 651-52 (redirect). Although he does not have any "hard data to prove that it works," he stated that during the previous 10 years none of his pre-treated patients experienced a deterioration of mitochondrial function.[133] Tr. at 223-25; *see also* Tr. at 660-62. He stated that before he was comfortable clinically with the "idea of offering Singulair as a mechanism to protect" he might have advised parents to "wait until two years," because it is "very uncommon" to see a regression past that point."[134] Tr. at 228. Now, all of his patients with mitochondrial disease get vaccinations. Tr. at 228.

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[130] The size of the "window" changed a few times. For example, in his report following his initial evaluation of A.A. on April 8, 2003, Dr. Kelley wrote that the period was "between 12 and 36 months." Pet. Ex. 6, p. 5 (emphasis added). In a July 14, 2003 letter exempting A.A. from further vaccinations he stated that the "window of greatest vulnerability for brain injury in children with [A.A.]'s type of metabolic disorder" was "at least six years old." Pet. Ex. 11, p. 126 (emphasis added).

[131] Unfortunately, Dr. Kelley did not elaborate on this concept or discuss the two articles he referenced during his testimony in any meaningful detail. Tr. at 213-17 (citing Henneberry, Pet. Ex. 41; M. Johnson, et al., *Neurobiology of Rett syndrome: a genetic disorder of synapse development*, BRAIN DEV., 23 Suppl. 1: S206-13 (2001), filed as Pet. Ex. 46 [hereinafter "Johnson, Pet. Ex. 46"]); *see also* Tr. at 287-88 (court examination).

[132] According to Dr. Kelley, Singulair "partially blocks . . . the cytokine cascade[;] it's thought to preserve immunity to protect the child and, yet, . . . attenuate the inflammatory response that is generally recognized in mitochondrial disease and other metabolic abnormalities." Tr. at 652.

[133] On cross examination, Dr. Kelley stated that he does not perform antibody titers on the children to test their immune response. Tr. at 660. He acknowledged that the "non-effect" could be due to the vaccination not causing the harm in the first place. Tr. at 661-62.

[134] Doctor Kelley could not recall his recommendation for A.A. Tr. at 226-27. In a letter dated July 14, 2003, Dr. Kelly excused A.A. from further vaccination due to her condition. The letter stated that A.A. "has autistic spectrum disorder and biochemical evidence of a mitochondrial disease." It explained that

Doctor Kelley was asked how many cases of regressive autism he has attributed to the MMR vaccine. Tr. at 225. He responded that he could remember only four cases "for sure." Tr. at 225. He continued that when has made such attribution,

> it's usually in the window when the MMR is given and . . . the timing is appropriate. Based on what is known about the immune response to the MMR vaccine, the . . . cytokine response . . . peaks at about 14 days and it's – in contrast to a child like [child's first name] Poling, who regressed almost immediately when she was given a lot of inflammatory vaccines, the few children that I've seen who have regressed with – based on evidence that they've regressed with the MMR, it was at 10 to 14 days after the immunization, which . . . [coincides with] the peak cytokine response[.]

Tr. at 225; *see also* Tr. at 279-81 (redirect). He commented that it was "surprising" how a live virus vaccine, which "is supposed to mimic infection" and stimulate the immune system "can cause such high levels of cytokines." Tr. at 225; *see also* Tr. at 648 (redirect). "Sometimes children get fevers, but it's presumably not in the fever-producing cytokines where the susceptibility occurs." Tr. at 225-26.

At the end of his direct testimony, Dr. Kelley affirmed that it was his opinion that the MMR vaccine substantially contributed to the onset of A.A.'s regressive autism. Tr. at 229. He stated that his opinion was largely based on the timing, which "makes sense in terms of the . . . pathophysiologic mechanism that we were beginning to develop at that time." Tr. at 229. He also stated that "she had clear signs of mitochondrial dysfunction." Tr. at 229. He continued: "I felt . . . as I said in my report, that this is a very good story . . . based on the timing and the known phenomenology of the immune system and mitochondrial interaction, this was a consistent story." Tr. at 229. In his opinion, the probability was high that the vaccine "was contributory. I'll put it that way at least. So, that was my opinion at the time." Tr. at 229.

On cross examination, Dr. Kelley clarified that he used the terms autism secondary to mitochondrial disease, mitochondrial PDD, and mitochondrial autism synonymously. Tr. at 236-37. He confirmed that "mitochondrial autism" is not a nationally or internationally recognized condition and is not used outside of the Kennedy Krieger Institute, but noted that the "association of mitochondrial disease with autism is quite well recognized." Tr. at 237.

Doctor Kelley was cross-examined about various parts of his expert report. Tr. at 241-42. He first was asked to explain what he meant when he stated that he had found

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"the physiological stress of a vaccine" can trigger the "onset of brain injury in children with mitochondrial disease. . . as was the case for [A.A.] at the time of her MMR immunization." Pet. Ex. 11, p. 162. For this reason, it was recommended that A.A. not receive any further vaccines until she passed "the window of greatest vulnerability for brain injury," which in children with A.A.'s "type of metabolic disorder" is six years of age. *Id.*

"convincing biochemical and clinical evidence for a primary or secondary mitochondrial disorder." Tr. at 242. He stated that it was a "combination of things," including the amino acid profile, the increased creatine kinase, the lactate level, the AST-ALT ratio, and the other biochemical criteria that he discussed during the hearing. Tr. at 242. In response to continued questioning, Dr. Kelley acknowledged that A.A.'s plasma lactate level was only borderline and that her struggling during the test could have been the cause of the elevation. Tr. at 242-45 (citing Pet. Ex. 6, pp. 4, 19). He also confirmed that he viewed the AST-ALT ratio as an indirect marker. Tr. at 245.

He was then asked about his citation to the Weissman paper [Pet. Ex. 28] as support for his assertion that "a combined increase in the plasma levels of alanine and glycine in a child with other clinical and biochemical signs of mitochondrial dysfunction and regressive autism always proves on muscle biopsy to be a deficiency of Complex I or Complex [I and] III." Tr. at 246. Doctor Kelley was a co-author of the article.[135] Tr. at 247. When pressed to show where he found support in the article for his assertion, he stated: "I don't believe that was in the article." Tr. at 247. Doctor Kelley conceded that his statement about muscle biopsy was supported only by his own experience and not on anything that has been published. Tr. at 248. He explained that he has had "maybe between half a dozen and ten patients who had a muscle biopsy, who [he] tested at some point, found to have that amino acid abnormality, they correlated." Tr. at 248. He continued: "So, the N was not enormous. It's difficult to generate large Ns in that setting, but the statement holds that it correlated." Tr. at 248.

As for the "convincing clinical evidence" of a "mitochondrial disorder," Dr. Kelley pointed to A.A.'s regression "under an inflammatory event," as well as her seizures and "some neuromotor abnormalities that you wouldn't expect in typical autism that may reflect some brain injury." Tr. at 249-50. He stated, however, that he did not "have the fullest understanding of her as a patient, because that was not [his] focus. It was on the biochemical testing." Tr. at 250. Indeed, he only saw her as a patient one time. Tr. at 250.

Doctor Kelley was also asked about the assertion in his report that A.A. "meets biochemical criteria for the diagnosis of a functional Complex I deficiency"—specifically, to which criteria he referring. Tr. at 250. He responded that it was the "strong correlation between the amino acid profile and . . . [his] association of that with the mitochondrial abnormalities." Tr. at 250-51. When asked what published criteria he was looking at when he made that statement, he conceded that he "go[es] beyond what is published." Tr. at 251. When pressed further, he conceded that his assertion was based only on his own criteria and that he was not aware of any nationally or internationally accepted criteria under which A.A. would be known to have a

[135] In response to my questioning, Dr. Kelley confirmed that there was a dispute among the authors regarding the inclusion of the paragraph discussing recent "increased concern" over "a possible causative role of vaccinations in autistic children with an underlying mitochondrial cytopathy." Tr. at 259-61 (citing Weissman, Pet. Ex. 28, at 4). The paragraph goes on to conclude that "[l]arge, population-based studies will be needed to identify a possible relationship of vaccination with autistic regression in persons with mitochondrial cytopathies." Weissman, Pet. Ex. 28, at 4.

mitochondrial disease. Tr. at 251-52. He stated that he does not use criteria such as Walker and Bernier, but guessed that "she would not meet those criteria."[136] Tr. at 252.

Doctor Kelley was asked to what he was referring when he stated that A.A. had a "chronic genetic mitochondrial disorder," since there was no evidence of a genetic defect. Tr. at 252-53. He responded that the statement was based on his assessment of her biochemistry—"there is no explanation for that other than a genetic deficiency that affects mitochondrial function." Tr. at 252.

Finally, Dr. Kelley was asked to explain what he meant when he stated at the conclusion of his report that in mitochondrial autism, the injury is triggered, but the disease is not. Tr. at 256. He partially answered that the injury was the regression, because "a regression that leaves the child . . . with permanent neurological deficits is a brain injury." Tr. at 256.

During another line of questioning on cross examination, Dr. Kelley was asked to discuss the significance of timing to his theory that the MMR vaccine caused A.A.'s regression, which he characterized as acute. Tr. at 253, 255. He stated that timing was "the most important thing." Tr. at 253. He elaborated that the "sequence of events" in this case were "compatible with the known . . . alterations in the inflammatory response that the vaccine causes," referring to the increase in cytokines levels. Tr. at 253-54; *see also* Tr. at 279-81 (redirect). He was then asked what his opinion would be if the regression had occurred one month later, instead of one to two weeks. Tr. at 254. Doctor Kelley stated that "the small number of cases I know, the onset of regression was . . . between seven and 14 days." Tr. at 254. However, he claimed that the "cytokine response continues for a couple months," but he could not "remember the details of the other patients to be able to say whether they continued to get worse." Tr. at 254. When asked whether he would still attribute causation to the vaccine if there was an intervening viral infection or ear infection, he stated that "it's not the infection, per se; it's the inflammatory response that could be used by either infection or a virus – or a vaccine." Tr. at 254-55.

Doctor Kelley was questioned also about the factual predicate for his evaluation and subsequent opinion: that A.A. had a loss of language, visual contact, and normal social interaction within one to two weeks following her MMR vaccination. Tr. at 255. He indicated (like Dr. Zimmerman had) that he relied on the history reported to him by A.A.'s parents and also contained in Dr. Zimmerman's records. Tr. at 255-56. When further pressed, he conceded that there was nothing specific in the medical records to indicate that a regression occurred during the alleged time frame. Tr. at 256-57. He stated: "I accepted that information as part of my data-gathering, and in trying to figure

[136] On redirect examination, Dr. Kelley stated criteria such as Walker focus on "more severe" and "known" mitochondrial diseases. Tr. at 273-74. Consequently, he does not "find any clinical value in [his] patient population," so he does not use them." Tr. at 275. He stated that "most patients, like [A.A.], would not meet those criteria because they're skewed toward the severe side." Tr. at 275; *see also* Tr. at 278-79.

out if she had a mitochondrial disease or not, I didn't delve into the timing. I trust Dr. Zimmerman." Tr. at 257.

Finally, Dr. Kelley was asked on cross examination to further elaborate on why he was able to attribute the MMR vaccine as the cause of the four cases of regression he discussed earlier. Tr. at 257. Unfortunately, he again had difficulty providing a responsive, straightforward answer:

> Just as a comparison or the basis for my feeling that is – fortunately, we don't have the DPT vaccine anymore, and many years ago, when that – before the – the DTaP, the acellular pertussis vaccine was available, I was aware of cases of regression that occurred immediately on vaccination, like [child's first name] Poling, who had multiple vaccines and had an acute inflammatory response. The cases I know where the MMR was suspected to be the cause, the timing was – the timing parallels the cytokine – the established – the known cytokine profile. So, that's like a normal – like a natural infection, and the immune response builds over a period of time. And we understand from the – what effect the inflammatory response has on mitochondria, that it's the cytokine response – the cytokine profile, the cytokine response of an infection that determines whether or not it will impair mitochondrial function. So, you will not expect a regression to occur with an MMR vaccine in the first few days, unless it w[as] given with another vaccine.

Tr. at 257-58. In response to follow-up questions, Dr. Kelley agreed that it was the timing that was most persuasive to him. Tr. at 258; *see also* Tr. at 285 (redirect). When asked if he would ever consider a regression in such circumstance to be coincidental, he responded that he would, but only if there had been another inflammatory event. Tr. at 258. He stated, however, that he would not be able to differentiate between inflammatory events, so it would still depend on timing.[137] Tr. at 258-59.

I asked Dr. Kelley to clarify whether he considered regression to be a brain injury. Tr. at 261. He responded that an acute regression "can be a brain injury or it can be a brain disturbance"—if the child does not recover, then it is a brain injury. Tr. at 261; *see also* Tr. at 256 (cross). I also asked to clarify whether, in his view, a regression could occur without any inciting agent. Tr. at 261-63. In response, he seemed to indicate that a "stressor" is necessary. Tr. at 261-63. He stated that regressions do not "come out of the blue," it is just "that we are not always able to identify what the stressor is." Tr. at 262.

[137] In response to my questioning on this topic, Dr. Kelley elaborated that if there "were another illness that caused an inflammatory response, which probably would increase TNF-alpha, then, yes, if there were another illness superimposed on that time window, then, indeed, one could not separate the two, because it's not specific." Tr. at 268.

In response to my further questioning, Dr. Kelley agreed that it was his view that "almost all regressive autism . . . [is] associated with mitochondrial dysfunction." Tr. at 269. After further discussion, I questioned whether he was aware of any epidemiologic study of regression in autism and mitochondrial disorders that has equated all or most regression to a mitochondrial problem. Tr. at 271. He responded "no," and then explained "there are articles that say a child has autism and mitochondrial disease, but unfortunately, . . . not all papers separate out one from the other," and "they are usually not segregated into regressive versus nonregressive." Tr. at 271; *see also* Tr. at 281-82. He commented that he had planned to do such a study. Tr. at 271-72.

I then tried to have Dr. Kelley discuss several articles he submitted in support of his theory that inflammation from the MMR vaccine caused or contributed to A.A.'s regression. Tr. at 264-68.[138] After an unfruitful attempt to elicit how each article related to A.A.'s case, Dr. Kelley stated:

> Yeah, I guess it's not that I would cite to a particular article for – in [A.A.'s] case. The – I have – one has to look at the larger picture. I have a – a common phenomenon that I see in – as regressive autism – associated with regressive autism in mitochondrial disease, and searching for explanations for that, then I come upon data that talks about cytokine response. So, I can't – what is most convincing to me in terms of the pathophysiology is TNF-alpha, but it is mostly the fact that the – for [A.A.'s] case in particular, it's not so much that – it's the simple observation that a vaccine is designed to cause an inflammatory response, and the timing of that inflammatory response is different in a DPT vaccine. That's all it is."

Tr. at 267-68.

At the conclusion of Dr. Kelley's testimony, I stated that over the years I have heard testimony from many different clinicians about various different treatments purported to improve autism—from secretin to chelation to methylcobalamin injections. Tr. at 668. I confessed that some of his testimony seemed in a similar vein. Tr. at 668. Doctor Kelley responded that his testimony should be credited based on his 25 years of experience "running a laboratory that's considered an international standard for this kind of work," his credentials, and the fact that he had given me "hard data, not just clinical observation." Tr. at 668-69. He expressed significant frustration over the difficulty he has encountered in publishing his methodology. Tr. at 669-72. He stated that he "fully appreciate[d my] skepticism because a lot of [his] colleagues feel that . . . you can't treat a mitochondrial problem." Tr. at 671. He concluded: "I'm a clinician and I can see my patients getting better on these treatments." Tr. at 672. This statement conflicted with

[138] The articles were: Poland, Pet. Ex. 71; A. Pukhalsky, et al., *Cytokine profile after rubella vaccine inoculation; evidence of the immunosuppressive effect of vaccination*, MEDIAT. INFLAMM., 12 (4): 203-07 (2003), filed as Pet. Ex. 54 [hereinafter "Pukhalsky, Pet. Ex. 54"]; R. Pons, et al., *Mitochondrial DNA abnormalities and autistic spectrum disorders*, PEDIATR, 144: 81-85 (2004), filed as Pet. Ex. 27 [hereinafter "Pons, Pet. Ex. 27"].

his testimony that he did not often retest patients after treatment, and did not account for a role for the other therapies that most children with autism receive.

3. Doctor Wiznitzer.

In his expert report, Dr. Wiznitzer opined that there was no support in the contemporaneous records for the alleged association, either causal or aggravating, between A.A.'s MMR vaccination and the occurrence of her ASD. Pet. Ex. K at 13. Rather, the evidence showed a developmental path consistent with ASD. *Id.* (citing R. Landa, *Diagnosis of autism spectrum disorders in the first 3 years of life*, NAT. CLIN. PRACT. NEUROL., 4: 138-47 (2008), filed as Res. Ex. O [hereinafter "Landa, Res. Ex. O"]). Of particular significance to his opinion was A.A.'s apparent language delay—an early manifestation of ASD—and the absence of contemporaneous medical evidence for a sudden regression following vaccination. *Id.*

Doctor Wiznitzer thought Dr. Kelley's causation opinion was inconsistent with the evidence. Pet. Ex. K at 14. In his view, A.A.'s mild language delay meant that she either did not have the mitochondrial dysfunction Dr. Kelley claimed, or its onset was prior to October 23, with a subacute evolution already present on that date. *Id.* at 14. He did not see an abrupt worsening of A.A.'s language. *Id.* at 14. Additionally, he found Dr. Kelley's opinion on the temporal relationship between A.A.'s vaccination and the onset of her ASD to be "purely speculative." *Id.* at 14. In his opinion, Dr. Kelley failed to account for the initial history of regression following A.A.'s ear infections. Doctor Kelley simply ignored multiple published studies that found no association between the MMR vaccine and autism, "including regressive autism." *Id.* at 14 (citing Institute of Medicine, IMMUNIZATION SAFETY REVIEW: VACCINES AND AUTISM (2004), filed as Res. Ex. P [hereinafter "2004 IOM Report, Res. Ex. P"], at 65-126.; T. Uchiyama, et al., *MMR-vaccine and regression in autism spectrum disorders: negative results presented from Japan*, J. AUTISM DEV. DISORD., 37: 210-17 (2007), filed as Res. Ex. Q [hereinafter "Uchiyama, Res. Ex. Q"]; D. Mrozek-Budzyn, et al., *Lack of association between measles-mumps-rubella vaccination and autism in children*, PEDIATR. INFECT. DIS. J., 29: 397-400 (2010), filed as Res. Ex. R [hereinafter "Mrozek-Budzyn, Res. Ex. R"]; Y. Uno, et al., *The combined measles, mumps, and rubella vaccines and the total number of vaccines are not associated with development of autism spectrum disorder: The first case-control study in Asia*, VACCINE, 30: 4292-98 (2012), filed as Res. Ex. S [hereinafter "Uno, Res. Ex. S"]).

At hearing, Dr. Wiznitzer testified, consistent with his expert report, that there was no evidence that A.A. regressed within one to two weeks after receiving the MMR vaccine or that the vaccine played any role in her developmental disabilities. Tr. at 485. Rather, her developmental trajectory changed by her 15-month checkup—something that the MMR vaccination neither caused nor aggravated. Tr. at 485-87, 515-17.

Doctor Wiznitzer began by explaining that the typical 15-month-old possesses one to three words for speech,[139] which are "above and beyond any kind of imitations and sounds that [the parent] might do." Tr. at 486. Additionally, such children have begun to walk, are "finger feeding," can wave goodbye, are interested in peekaboo and pat-a-cake games, can play with cause-and-effect toys, and have started to stack blocks. Tr. at 485. They also will reliably turn when called by name and can sometimes follow simple one-step commands. Tr. at 486.

Based on his review of the available records, Dr. Wiznitzer testified that A.A. had normal development during her first year and attained some of these milestones. Tr. at 485. However, by the time of her 15-month checkup, her developmental trajectory had changed and an apparent speech delay was present. Tr. at 486; *see also* Tr. at 610-11 (court examination). Indeed, it was his opinion that A.A.'s speech development was likely delayed even at her one-year checkup. He noted that although she reportedly had one to three words at that time, multiple later records indicated that she only "made animal sounds and maybe had one word" at that point. Tr. at 486; *compare, e.g.*, Pet. Ex. 9, p. 10 ("says 1-3 words") *with* Pet. Ex. 5, p. 5 ("said her first word 'Quack' at 1 year and speaking a little more/using animal sounds at 15 months"). He also saw evidence of language delay in the October 14 video recorded prior to her vaccination. In video segments taken at home, he observed that A.A. vocalized but used no words, including "ma-ma and da-da"—even though her parents were present. Tr. at 487 . He questioned whether A.A. was using these words with specificity, meaning that when she said "ma-ma," she did so in reference to her mother. She said no words during her visit to the pumpkin patch later that same day. Tr. at 480-90.

Additionally, Dr. Wiznitzer saw some "subtle" differences in her behavior from what would normally be expected from a developmental standpoint. Tr. at 487. For example, in the video she never raised her hands to be picked up from her crib, and when she stopped to look at a favorite stuffed animal, she flapped her hands—a motor mannerism or "stereotypy" commonly seen in autistic individuals and noted in later records by Dr. Zimmerman.[140] Tr. at 487-88; *see* Pet. Ex. 6, p. 21.

[139] In his expert report, he stated that at 15 months, "a child typically has 3-5 words and mature jargon with real words." Res. Ex. K at 13.

[140] On redirect, Dr. Zimmerman stated that he did not agree with Dr. Wiznitzer that A.A. exhibited hand-flapping in the video. Tr. at 676. He viewed the behavior as "normal movements with excitement for a child that age." *Id.* He stated that there were "some repetitive movements – arm movements such as when she was holding a couple of glass coasters and banging them together, but she did not have hand flapping." *Id.* He explained that "there is a fairly typical progression" in ASD—a "hierarchy of symptoms." *Id.* At onset there is "the loss of language and social skills," which is followed by "the repetitive movements, the circling behaviors and the hand flapping and jumping." *Id.* He stated that the behaviors in the video were "not like that and [he] would not have expected them" at that point. *Id.* It is unclear why he thought that the repetitive movements he identified in the video (*i.e.*, banging coasters) were normal as opposed to repetitive movements falling within the hierarchy of symptoms. Dr. Zimmerman later testified that stereotypies, including repetitive behaviors, hand flapping, and circling movements, can present before the loss of language, "but this would be very unusual." Tr. at 681 (recross).

On cross examination, Dr. Wiznitzer acknowledged that A.A. was interactive with her parents in the October 14 video, but he found the quality and level of her interaction to be mildly diminished. Tr. at 529. For instance, although she was seen handing her mother a toy, running back and forth around the house, and making eye contact (at least with the camera), she did not hug her parents or raise her hands to be picked up. Tr. at 529. He stated that the real question was whether this was the type of interaction "normally expected . . . or was it mildly diminished as we see in some of the studies [where] children gradually evolve into the autistic clinical picture." Tr. at 529-30.

In his view, A.A.'s lack of spoken functional words,[141] her disinterest in being lifted from her crib, and her distinctive motor mannerisms, were indicative of existing developmental problems and early signs of autism. Tr. at 488-89; *see also* Tr. at 500-01 (direct); 603-04 (court examination). As a consequence, Dr. Wiznitzer disagreed with Dr. Zimmerman that A.A. was developmentally normal on October 14, a few days before her vaccination. Tr. at 486-87.

With regard to A.A.'s post-vaccination condition, Dr. Wiznitzer stated that nothing in the contemporaneous medical evidence reflected an adverse vaccine reaction or an abrupt deterioration of her development.[142] Tr. at 491. Indeed, A.A. did not have a return medical visit for nearly two months, until December 18, when she was treated for a respiratory infection and ear infection. Tr. at 496. Nothing in the record from that visit referenced any loss of skills or other significant change. Tr. at 496-97 (citing Pet. Ex. 9, p. 59). Doctor Wiznitzer viewed this as a clear indication that the vaccine had no adverse impact on A.A.'s health or development. He stated that in his experience, when parents see something different in their child, they come in for an office visit and bring up the problem. He was confident "that if there was a concern . . . going on at that time, it would have been identified." Tr. at 496-97.

Doctor Wiznitzer noted that another opportunity to identify an adverse reaction was on April 2, 2001, when A.A. visited her doctor and received additional vaccinations. Tr. at 515; *see* Pet. Ex. 9, p. 1. He explained that physicians typically ask parents about problems with prior vaccinations before they administer others, and will document the parents' response. Tr. at 515-16. Nothing was noted in A.A.'s record about an adverse reaction following her October 23 vaccination. Neither was anything noted when she visited her doctor a month earlier, in March 2001. Tr. at 516; *see* Pet. Ex. 9, pp. 8, 18, 56. Doctor Wiznitzer also found no documentation of any phone calls from A.A.'s parents reporting a fever or similar concern, which was curious since they did not hesitate to contact the physician and bring her in for an appointment at other times when she had fever or was ill. Tr. at 516.

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[141] Doctor Wiznitzer distinguished functional words from "just repeating animal sounds" or "holding up a finger" to show one's age. To illustrate his point, he noted a clip from the video that showed A.A. responding to the question of her age with the incorrect script—she answered with the "how big" gesture, rather than the raised finger. Tr. at 488-89; *see also* Tr. at 603-04 (cross).

[142] He noted that even records created months after the vaccination contained no notations regarding regression. Tr. at 491.

Doctor Wiznitzer likewise found no indication in the contemporaneous records that A.A. had a speech regression within two weeks of her vaccination. Tr. at 493. He explained that speech regression[143] in autism is the loss of between three and five functional words—words "that the child is using for functional purposes [and] have persisted for at least one month." Tr. at 492. He emphasized that such words are in addition to "the specific ma-ma and da-da."[144] Tr. at 492. Based on the evidence, he was doubtful that A.A. had three to five functional words to lose.[145] Tr. at 523, 552.

On cross examination, Dr. Wiznitzer challenged Ms. Edick's assertion that "a 15-month old has a vocabulary of 10 to 24 words" as an incorrect statement—"[a] special education teacher shouldn't say that."[146] Tr. at 535. Doctor Wiznitzer explained that it would be "highly, highly unlikely" for a child that age to have such a vocabulary due to the way language develops and also "the immaturity of the oral motor mechanism in terms of verbalization." Tr. at 535-36. He stated that in his many years of practice he could not recall ever meeting a child who had 24 words at 15 months of age—"functional words that they use independently." Tr. at 536.

Doctor Wiznitzer also reviewed and discussed the October 29 video taken at the Halloween event, which allegedly showed significant post-vaccination behavioral changes. Contrary to petitioners' view, he saw no evidence in the video of the alleged regression, or any other significant behavioral issues. Tr. at 493, 495. For an equivalent comparison, he focused on A.A.'s behavior at the pumpkin patch on October 14 because both were "shot basically in the same environment." Tr. at 493. Her behavior on the two occasions was strikingly similar. Tr. at 495. At the pumpkin patch, for instance, she barely vocalized and seemed uncomfortable with her surroundings, although she did engage in some limited exploration. Tr. at 490, 531. Likewise, at the Halloween event, she was quiet and appeared unsettled with the "hubbub" and commotion of the crowd. Tr. at 494. Doctor Wiznitzer also noted that she responded to

[143] Doctor Wiznitzer explained that speech regression is different from speech delay. The latter "is failure to have adequate language development[.] . . . It's not that you've lost words; it's that [language] does not develop the way it should." Tr. at 492. To illustrate his point, he described "children with speech delay who may have some word utterances for a few days and then lose those words." Tr. at 493. Such an event is not speech regression; instead it is an instance of someone having taught the child to repeat certain words, but because they held no functional purpose, they faded. Tr. at 493.

[144] Doctor Wiznitzer explained that "ma-ma" and "da-da" are excluded because parents can "confuse[] the nonspecific babble with the specific terms." Tr. at 492.

[145] On redirect, Dr. Zimmerman stated that he disagreed that A.A. had no functional words to lose—she had "moo." Tr. at 677.

[146] As a school-based special education teacher, Ms. Edick would not have much contact with children under the age of three in a teacher-student setting. Early intervention programs provide treatment for children with developmental delays and neurodevelopmental disorders such as ASD up to three years of age. At that point, the children transition to services provided through the school system. A.A. similarly transitioned to school-based programs at three years of age. Tr. at 87, 89, 548; Pet. Ex. 7, p. 10. (preschool at Village Green Day School in the fall of 2001).

her name on both occasions, although inconsistently.[147] Tr. at 532; *see also* Tr. at 611-12.

However, Dr. Wiznitzer saw "a clear difference" in her behavior and social interactions when she was in the familiar surroundings of home as compared to outside in public. Tr. at 490; *see also* Tr. at 604-05 (court examination). For instance, as seen in the October 14 video clips taken at home, A.A. comfortably babbled, laughed, and interacted with her parents; whereas later that same day, at the pumpkin patch, she vocalized very little and was much less active. Tr. at 490, 533. He explained that such reticent behavior was not unusual or necessarily concerning from a developmental standpoint, as children at this age often feel "stranger anxiety" and vary in the time needed to acclimate to a given situation. Tr. at 490. Available medical records "described her as shy, suggesting that she required a bit more time to acclimate in comparison to the average child." Tr. at 490-91. According to Dr. Wiznitzer, what was important from a developmental perspective was A.A.'s evident awareness of her surroundings and the people around her—she was just "a bit overwhelmed by what [was] going on." Tr. at 494, 533.

In response to my questions, Dr. Wiznitzer discussed the video clips taken between Christmas Day and December 30. Tr. at 605-08. He stated that by Christmastime "there was clearly a change." Tr. at 606. He observed that she was not making good eye contact; she was not vocalizing; and she had decreased interaction. Tr. at 605. She was also "still doing some cause/effect play," but it was less than the play seen in the October 14 video. Tr. at 605. He even observed a difference between the October 29 video and the Christmas Day video, noting that on the earlier occasion she "did the appropriate thing" with the beanbag game—put the beanbag through the hole—whereas on Christmas she had no real interest in the toys and was seen flicking a string instead. Tr. at 606. Doctor Wiznitzer, however, was unable to state, based on the videos alone, that there was a continuum of deterioration between October and December. Tr. at 608. This was because the videos were shot in different environments. Tr. at 608.

On cross examination, Dr. Wiznitzer was questioned further about the timeline of A.A.'s autistic presentation. Tr. at 541-49. He agreed that "around Christmastime" it became clear that there was "something not right" about A.A.'s behavior. Tr. 541-42. He also agreed with the basic timeline of events thereafter leading up to her formal diagnosis; however, he disputed that it took 15 months for her to receive a diagnosis. Tr. at 549. Rather, he calculated that nine months elapsed between her Christmastime behavior and Dr. Lavenstein's note that she had "autistic symptomology." Tr. at 549 (citing Pet. Ex. 9, p. 96).

Doctor Wiznitzer was also questioned about Ms. Edick's testimony concerning A.A.'s behavior on Veterans' Day weekend. Tr. at 537-41. He found it difficult to place

[147] Doctor Wiznitzer explained that A.A.'s inconsistency in responding to her name was typical "kiddie behavior." Tr. at 611. However, if that behavior was consistent, it would be a "red flag." *Id.*

significant weight on her recollections, as the events she described occurred many years earlier and were uncorroborated by any independent documentation. Tr. at 537-38, 540. He indicated that he did not doubt Ms. Edick's observations, but whether they occurred at the times she remembered them occurring. Tr. at 538-41. He explained that in his clinical experience, when patients relate a history they will often be more accurate when the event is close in time. Tr. at 538-39. As time passes, "there can be some distortion of the information either in terms of telescoping, putting it into a different time zone, or not necessarily appreciating some of the important facts or points that were there." Tr. at 539; *see also* Tr. at 614-16 (court examination).

In his view, A.A.'s abnormalities in speech and behavior were present prior to her vaccination and were early signs of autism. Tr. at 500-01. Doctor Wiznitzer explained that autism spectrum disorder is a "neurodevelopmental condition that impacts adversely on socialization and social communication and has associated restrictiveness and repetitive behaviors with onset in the early childhood years." Tr. at 497. He stated that "presentation is usually between age one and two years," but symptoms are always present before age three years. Tr. at 497. Although presentation varies, speech delay is the "most common" complaint from parents. Tr. at 497-98. Other symptoms include decreased eye contact and changes in social behavior. Tr. at 498.

Doctor Wiznitzer then described three common ASD presentation types. In one group, the symptoms are not obvious at the time, but are apparent in retrospect. Tr. at 498. In such cases, parents often begin to see differences between the functioning of their child and that of their child's normal peers, especially in the area of language development. Tr. at 498. When these parents look back, they realize that their child has been symptomatic from early- to mid-infancy. Tr. at 498. In a second group, the children seem to be functioning "at or near normal for about the first year to two years of life, [but] then [undergo] a stagnation of their development"—they "don't seem to move to the next developmental level." Tr. at 498. Such children might, for example, fail to transition from the "sociability stage, which is like smiling . . . at people, having some interest in looking at them, to more active interactions and interventions, in going up to them." Tr. at 498. The third group consists of children who "appear to have normal developmental progression and then actually have a true regression of skills." Tr. at 499. In those children, the regression "could first start as a speech regression, but quickly gets linked with a speech and social skills regression." Tr. at 499.

In response to my questions, Dr. Wiznitzer elaborated that regression in autism is not an abrupt occurrence. Tr. at 597-602. He explained that the loss of language and social skills typically "evolve[s] over a period of weeks to a period of months."[148] Tr. at 600-01. He stated that "an overnight story" would lead him to "start looking for other disorders." Tr. at 601.

[148] Doctor Wiznitzer defined a "gradual onset" as taking months, and an "abrupt onset" as taking weeks. Tr. at 601. He stated that the loss of skills is usually gradual—over a period of "a month or two." Tr. at 602.

Doctor Wiznitzer agreed with A.A.'s ASD diagnosis, which he found supported by the records. Tr. at 499. He elaborated that the "records in 2001 and afterwards clearly tell us that she has . . . features consistent with that diagnosis. She has . . . impairment in socialization, and impairment in pragmatic skills, [and] impairment in social communication." Tr. at 499. Repeatedly, she met the diagnostic criteria for ASD in established rating scales. Tr. at 499.

According to Dr. Wiznitzer, A.A.'s autistic presentation was not atypical; it fell within the expected range. Tr. at 500. Moreover, even "a relatively rapid regression"—which was not shown—would still be "within the framework of what's been described for the population." Tr. at 500.

Doctor Wiznitzer discussed potential causes of autism, including whether vaccines are known to play a role. He explained that the disorder is biologically based, with "a strong genetic component." Tr. at 501. The "vast majority have or will be shown to have underlying genetic problems with genes that influence brain development."[149] Tr. at 501. Others can be affected by "insults to the brain prenatally, perhaps due to some toxic agent," such as valproate or excessive alcohol exposure. Tr. at 501. Prematurity has also been described, although it is yet unclear whether it is the prematurity itself or some gene abnormality that is responsible for the autistic phenotype[150] in such children. Tr. at 501. He acknowledged the association between primary mitochondrial disease and ASD, which has been reported in the literature, but stated that there is no known connection between vaccination and autism. Tr. at 502-03. Ultimately, the underlying cause of ASD is not always known. Tr. at 501.

Doctor Wiznitzer then addressed Dr. Kelley's theory that the MMR vaccine causes a TNF-α-mediated inflammatory response, which can lead to autistic regression in individuals with mitochondrial abnormalities. Tr. at 503. Of importance to Dr. Wiznitzer were two articles cited by Dr. Kelley as support for this theory. The first study examined the immune response related to immunosuppression in subjects vaccinated with live attenuated rubella vaccine. A. Pukhalsky, et al., *Cytokine profile after rubella vaccine inoculation; evidence of the immunosuppressive effect of vaccination*, MEDIAT. INFLAMM., 12 (4): 203-07 (2003), filed as Pet. Ex. 54 [hereinafter "Pukhalsky, Pet. Ex. 54"]. The second study focused on the cytokine production profile of children following the first and second doses of the measles vaccine. Poland, Pet. Ex. 71. In his view, neither article supported Dr. Kelley's hypothesis regarding the inflammatory effect of vaccines. Tr. at 506, 510.

With regard to the Pukhalsky article, Dr. Wiznitzer first commented on its title, which he noted "does not say immune-inflammatory effect but immunosuppressive

[149] He recalled Dr. Zimmerman's testimony regarding synaptic development as an example. Tr. at 501.

[150] Doctor Wiznitzer defined "phenotype" as "the clinical picture." Tr. at 502.

effect." Tr. at 504. He explained that cytokines[151] have a "variety of jobs" and not all are pro-inflammatory.[152] Tr. at 504, 593. In this study, the researchers analyzed the levels of certain cytokines following vaccination, including interleukin (IL)-4, tumor necrosis factor alpha (TNF-α), and interleukin (IL)-10. Their results showed that IL-4 levels remained essentially the same seven days after vaccine inoculation—they were "no different than . . . at baseline." Tr. at 504-05 (citing Fig. 2). Their results also showed the interplay between IL-10 (an anti-inflammatory cytokine) and TNF-α (a pro-inflammatory cytokine). Tr. at 505 (citing Fig. 3). The researchers found that, at seven days post-vaccination, there was "no significant rise in the TNF-[α] value, which means there should be no increased risk of inflammation compared to baseline." Tr. at 505. There was, however, a significant rise in IL-10, which suggested that "at that time [there] may [have been] a bit more anti-inflammation compared to inflammation." Tr. at 505. And then "at 30 days out, basically there's much more anti-inflammation compared to inflammation, which is why the article [was titled] the immunosuppressive effect." Tr. at 505-06. He concluded that the article did "not support Dr. Kelley's hypothesis that within one to two weeks there is a significant rise in TNF-alpha." Tr. at 506. "[I]n fact, you can make an argument that this article tells us that the rise in IL-10 would actually tame the inflammatory process." Tr. at 506.

Doctor Wiznitzer then discussed the Poland article, which also examined cytokine levels following vaccination. Tr. at 506-10; *see also* Tr. at 588-95 (cross). The study analyzed cytokine secretion and plasma levels of six cytokines in two groups of children following measles vaccination. The first group consisted of 12-15 month-old toddlers receiving their first measles vaccination, and the second group was composed of children aged 4-12 years receiving a second dose. Measurements were taken prior to vaccination to obtain a baseline and then at regular intervals thereafter, to 40 days. Tr. at 507. Doctor Wiznitzer focused on the results of the first group because the children were analogous to A.A. in age and circumstance (*i.e.*, first dose of a vaccine). Tr. at 508. He began with figure 1(A),[153] which showed that for the first 15 days following vaccination—the critical time period according to Dr. Kelley—none of the

[151] Cytokine is "a generic term for non-antibody proteins released by one cell population (*e.g.*, primed T lymphocytes) on contact with specific antigen, which act as intercellular mediators, as in the generation of an immune response." DORLAND'S at 466.

[152] According to Dr. Wiznitzer, "Dr. Kelley represented IL-4 as a pro-inflammatory substance." Tr. at 594. Petitioners' counsel disagreed with his recollection. *Id.* In his testimony, Dr. Kelley grouped IL-4 with "dozens" of other "factors that will be sent out" in response to infection, including IL-6 and TNF-α. Tr. at 219. During this portion of testimony, Dr. Kelley went on to discuss how various studies have "shown what the cytokine response is in this infection or that immunization," but stated "correlations have not been made as to . . . what combination of cytokines are most likely to impair mitochondrial function." Tr. at 219. Although he did not specifically identify IL-4 as "pro-inflammatory," his comments implied that he viewed IL-4 as such, and are thus illustrative of the challenges posed by his imprecise and rambling testimony.

[153] Doctor Wiznitzer explained that the results shown in figure 1(A) were obtained from white blood cells that were secreting cytokines. Tr. at 594-95. The researchers then "took the supernatant, which is the fluid around the cells, and analyzed it for concentration of the cytokines." Tr. at 595.

values for IL-4, IL-6, or TNF-α secretion rose above their baseline.[154] Tr. at 508. "In fact, at two weeks afterwards, IL-6 and . . . TNF-alpha [fell] below their baseline values [, and] IL-4 basically [did not] change to any significance." Tr. at 508; *see also* Tr. at 590-94 (cross). Similarly, the values in figure 2(A), which reflected plasma cytokine levels at regular intervals, remained fairly steady. Tr. at 509. Specifically, there was no appreciable change in the blood levels of IL-6 and TNF-α over time, and IL-4 fluctuated up and down. Tr. at 509-10. He noted that "the paper itself state[d] that there was no appreciable change in the cytokine levels" for the toddler group. Tr. at 510.

In summary, Dr. Wiznitzer stated that "the two articles that Dr. Kelley brought to the Court and cited do not support his proposition that IL-4, IL-6, or TNF-alpha levels in the blood or in cell culture rise within two weeks of a vaccination, which means that that can't be the mechanism of this purported injury." Tr. at 510.

Doctor Wiznitzer also expressed significant concerns with the "very unclear" methodology Dr. Kelley used to interpret A.A.'s amino acid test results. Tr. at 510. He directed attention to Pet. Ex. 23A, the spreadsheet summary of A.A.'s amino acid profile, which Dr. Kelley used to show that A.A. met the biochemical criteria for a functional complex I deficiency diagnosis. Tr. at 511. His first concern related to the calculation of the range and mean values. Doctor Wiznitzer stated that it appeared, based on his own calculations, that Dr. Kelley had taken the minimum range value plus the maximum range value and divided by two, "which means [that] his lab . . . has a perfect bell-shaped curve of data." Tr. at 511. He stated that this "only happens in articles and problems that are given to students . . . . In the real world, there's always either a shift to the right or a little . . . shift to the left. You're not exactly in the middle every single time." Tr. at 511. He further noted that Dr. Kelley's sample size was 100, which is too small to obtain a perfect bell curve. Tr. at 513.

His second concern related to the "normalized ratios to mean normal," which was noted on the spreadsheet as "0.8 to 1.2." Tr. at 513. Doctor Wiznitzer stated that Dr. Kelley again "doesn't tell us how that normal was calculated. He basically says trust me; that's because I found it to be this way." Tr. at 513. Doctor Wiznitzer then performed an example calculation using the values shown for the amino acid taurine. Tr. at 513. He explained that the resulting value would be considered "an outlier in this population, but yet it's still within the normal range"—an unusual outcome. Tr. at 513. He also took issue with Dr. Kelley's apparent comfort with standard deviations as great as 11.[155] Tr. at 513-14. The standard deviation for a normal range is usually "plus or minus two standard deviations." Tr. at 514.

[154] On cross examination, Dr. Wiznitzer was asked whether the cytokine fluctuations that occurred between day zero and day 15, as shown in figure 1(A), were indicative of inflammation. Tr. at 591-94. He explained that although the levels of IL-6 and TNF-α fluctuated, they returned to baseline—and "baseline is not inflammation." Tr. at 594.

[155] Doctor Wiznitzer recalled Dr. Kelley's statement that "one of his lab values was 11 standard deviations above the mean." Tr. at 513-14 (*see* Tr. at 181). He found "it extremely hard to believe that any of these numbers are 11 standard deviations above the mean. That is an astronomically high number." Tr. at 514.

Doctor Wiznitzer's final concern related to the application of Dr. Kelley's normal range values to the test results from other labs. Tr. at 514. He cautioned that Dr. Kelley's assumption that the other labs' numbers were derived from historical data could be mistaken. Tr. at 514. In addition to fluctuations in testing between labs, the other labs could also have established their own normal ranges. Tr. at 514. So applying the values as he has done "can be fraught with problems." Tr. at 514.

As a consequence of these concerns, Dr. Wiznitzer found it difficult to "state that this information has any value." Tr. at 515. Without knowing "where these numbers came from," the validity of the values and resulting conclusions are completely suspect. Tr. at 515. "There's a lot of unanswered questions here . . . [a]nd those are only some of them." Tr. at 515.

On cross examination, Dr. Wiznitzer confirmed that he does not evaluate or diagnose mitochondrial disorders, but instead refers patients to colleagues who are mitochondrial specialists. Tr. at 549-50. He discussed the factors or clinical presentations which would lead him to provide a referral for a mitochondrial evaluation. Tr. at 550-51. He stated that he would likely refer for "unexplained lactic acidosis; unexplained multi-organ system disease; neuro-imaging abnormalities that could be consistent with a mitochondrial disorder, such as abnormal signal from the basil ganglia and white matter; abnormalities in amino acid metabolism, especially significantly elevated alanine; [and] intractable epilepsy that's not explainable." Tr. at 550. He would also refer for unexplained developmental delay and global regression, which he defined as regression in all skills.[156] Tr. at 552.

Doctor Wiznitzer typically would not refer an autistic child for a mitochondrial evaluation. Tr. at 554. He explained that he would look to standardized guidelines on the evaluation of children with autism. Tr. at 555-56. At a minimum he would order a chromosome micro array, a DNA test for fragile X syndrome, and a test for Rett syndrome (if the child was female). Tr. at 556. Then he would "look at the rest of the clinical scenario. So, if I have a child who clearly has a history of regression, I then start looking for potential underlying metabolic problems. And then I'll do the metabolic testing. But I don't do it for every child. That is not what's recommended in the guidelines." Tr. at 556. Dr. Wiznitzer stated that has "had children who present with autistic regression, clear-cut history of autistic regression, well-documented history of autistic regression. And I have done the full workup, which includes the metabolic workup." Tr. at 557. "I do that on a regular basis." Tr. at 557.

On cross examination, Dr. Wiznitzer was questioned about his heavy reliance on contemporaneous medical records and asked whether he had "totally discounted" the statements made by A.A.'s parents and aunt. Tr. at 521. Doctor Wiznitzer responded that he "never discount[ed] anything," but tried to place it in context. Tr. at 521. In his

[156] Doctor Wiznitzer disagreed that A.A. had a global regression. Tr. at 552. Rather, it was his opinion that she had a social regression consistent with autism. Tr. at 552.

view, statements made about unmemorable events many years earlier must be afforded less weight than contemporaneous accounts documented in the record. Tr. at 520. For example, with regard to A.A.'s alleged post-vaccination fever, he found it difficult to believe that her parents would not have reported it to her primary care provider when it occurred—especially when they did not previously hesitate to contact her physician for such matters. Tr. at 520. He expressed similar reservations "about the whole scenario, fever, speech regression, social regression, motor regression. These are serious problems, and I don't see [them] reflected in the medical records at all." Tr. at 521. I note that I was unable to note any contemporaneous medical record or history provided close in time to the period of alleged regression that reflected a loss of motor skills, notwithstanding Mr. Allen's testimony about A.A. crawling more than walking at one point after the vaccination. It was clear from his testimony that she had not lost the ability to walk at any point.

Doctor Wiznitzer was also cross-examined about A.A.'s post-vaccination regression. He reiterated that he had fully considered the statements and testimony of A.A.'s parents and aunt, but found them largely unsupported by the record. Tr. at 521-23. With regard to A.A.'s alleged regression of speech, he emphasized that based on the available records, "there was no speech to be lost." Tr. at 523. He noted that Dr. Lavenstein's initial report, for example, indicated that A.A. may have had some oral sounds but then subsequently regressed. Tr. at 523 (citing Pet. Ex. 9, p. 96 (primitive speech)). "That's not a speech regression; that's oral sounds. And even Dr. Lavenstein documented that she had no words. You can't have a speech regression if you have no words." Tr. at 523. Doctor Wiznitzer acknowledged that Dr. Lavenstein used the term "regression" for the loss of oral sounds, but emphasized that the "true definition of speech is not primitive sounds, it's not babbling." Tr. at 524, 553.

In response to additional questioning, Dr. Wiznitzer reviewed the medical record of A.A.'s one-year checkup, which indicated she said "1-3 words." Tr. at 524 (citing Pet. Ex. 9, p. 10). He acknowledged what the record reflected, but explained that a checked box is not that informative. For instance, "we don't know what those words were, we don't know how long they persisted, [and] we don't know if they lasted for more than a month, which is the criteria you need to use." Tr. at 525. Unfortunately, "[a]ll it says here is that she had words. There's no documentation of anything else." Tr. at 525. Doctor Wiznitzer saw this as an example of a "superficial" history, which failed to get to "the core information" because the clinician did not "dig deeper" and ask more than routine questions. Tr. at 525-26. He confessed that it can be difficult in the clinical setting to get good, detailed histories about language; however, they are vitally important, which is why the Autism Diagnostic Interview,[157] for example, asks such in-depth questions. Tr. at 528.

[157] The Autism Diagnostic Interview is a testing instrument used in "diagnosing autism, planning treatment, and distinguishing autism from other developmental disorders." *See* WPS (publisher), http://www.wpspublish.com/store/p/2645/autism-diagnostic-interview-revised-adi-r (last visited Sept. 10, 2015).

He found similar problems with the speech pathologist's report, which stated that A.A. "said her first word, quack, at one year and speaking a little more using animal sounds at 15 months." Tr. at 527 (quoting Pet. Ex. 5, p. 5). He explained that the phrase "speaking a little more" is ambiguous and therefore unhelpful because it gives no indication of the number and quality of words present at 15 months, which is an important piece of information for diagnostic purposes. Tr. at 528. Depending on the definition, a speech regression is the loss of "either three words or five words, besides ma-ma and da-da"—and "[t]here's no comment here about whether she ever used ma-ma and da-da."[158] Tr. at 528.

Doctor Wiznitzer contrasted these poorly obtained histories with the one elicited by Dr. Lavenstein, which he viewed as a good, well-documented example. Tr. at 526. Doctor Lavenstein's report provided a clear indication of the quality of A.A.'s "speech"—she "had oral sounds. He clearly had asked . . . the question, did your child have functional words, and the answer was no."[159] Tr. at 526.

On cross examination, Dr. Wiznitzer was asked whether children with metabolic problems are known to decompensate with infections. Tr. at 557. He indicated that decompensation can occur with certain kinds of metabolic disorders, but in general, it is not a concern. Tr. at 557. "It depends on the specific metabolic problem they have." Tr. at 557. He noted, for example, that patients with urea cycle disorders are susceptible to potentially deleterious effects, but children "with creatine transport deficiency don't fall apart . . . with infection . . . [y]et they have a metabolic disturbance." Tr. at 558-59.

Doctor Wiznitzer was then questioned about an article submitted by Doctor Cederbaum regarding the administration of vaccines to children with inborn errors of metabolism ["IEM"]. Tr. at 559-64, 587-88 (citing F. Menni, et al., *Vaccination in children with inborn errors of metabolism*, VACCINE, 30 (50): 7161-64 (2012), filed as Res. Ex. E [hereinafter "Menni, Res. Ex. E"]). The article stated that administering vaccines to children with IEMs "is not as simple as in healthy subjects because the vaccines themselves can cause problems. They can theoretically deteriorate the fragile metabolic equilibrium of affected children, particularly when they cause the same metabolic (albeit less severe) changes that are usually associated with the disease they are meant to prevent." Menni, Res. Ex. E at 7161-62. The article continued: "Vaccines should be administered more cautiously to children with IEMs associated with significant risk of morbidity and/or mortality with catabolic events: *i.e.*, under strict medical supervision, and only when the children are clinically well and their metabolic condition is acceptably controlled." *Id.* at 7163. It also noted that "[p]articular care should be

[158] Doctor Wiznitzer stated that he did not recall A.A. using "ma-ma" or "da-da" to refer to her parents in the video segments he watched. Tr. at 528.

[159] Doctor Wiznitzer indicated that if A.A.'s parents had told him that their child stopped talking, he would have inquired about the level of "talking" she had been doing—was she simply repeating what the parents said, was she making animal sounds, did she have functional words? He emphasized that "we need all that kind of information." Tr. at 526.

taken when administering vaccines based on live attenuated viruses because they can cause the same metabolic derangements as wild virus infections." *Id.*

Doctor Wiznitzer agreed with the authors' statements, but noted the word "theoretically"—"that doesn't say it will do it, it just says theoretically." Tr. at 560-61. He explained that the concern relates to the fact that "vaccines can cause fever and fever can make you catabolic." Tr. at 561. He stated that the authors were not referring to all metabolic disorders, but only those "that are at risk for morbidity when they go catabolic, such as amino acid disorders, organic acidemias, and urea cycle disorders." Tr. at 561. Moreover, it was not the immunization, but its timing that was important—it should be given when the child is well and her condition is controlled. Tr. at 562. In response to additional questioning, Dr. Wiznitzer confirmed that the MMR vaccine contains live attenuated virus, which is a weakened, "tamed down" version of the natural virus intended "provoke the immune response without provoking . . . a clinical infection." Tr. at 563-64.

Doctor Wiznitzer was also questioned about a study that was discussed in the Menni (Res. Ex. E) article. Tr. at 565-87 (citing N. Klein, et al., *Evaluation of Immunization Rates and Safety Among Children with Inborn Errors of Metabolism*, PEDIATRICS, 127: e1139-46 (2011), filed as Res. Ex. D [hereinafter "Klein, Res. Ex. D"]). The study focused on children with inherited metabolic disorders and sought to better understand immunization rates and vaccine safety within this population. Klein, Res. Ex. D at e1139. Data for the study was obtained from medical records contained in the Northern California Kaiser Permanente electronic database from 1990 to 2007. *Id.* Based on their analyses, the researchers found that vaccination of children with IEMs "was not associated with any significant increase in emergency department visits or hospitalizations during the 30 days after vaccination." *Id.* However, "[s]econdary analyses suggested that there may be increased rates of hospitalizations 2 weeks after vaccination for the sickest 1- to 4-year-old children." *Id.* The researchers concluded that "[i]mmunization was not associated with increased risk for serious adverse events during the month after vaccination," a finding that "provid[ed] overall reassurance that routine vaccination of children with [IEMs] does not result in adverse effects." *Id.*

Doctor Wiznitzer specifically addressed the researchers' secondary analyses, which indicated a possible increase in the rate of hospitalization for children in the "sickest" category. Tr. at 565. He first explained that the researchers' use of the word "may" indicated that the results did not reach statistical significance.[160] Tr. at 565-66. He then explained that the results of the secondary analyses provided "limited information about which to reach conclusions." Tr. at 571. This was due to the way the researchers reported their results. The researchers stated that "they found a modest increased risk of hospital admission" for the "sickest" children (Tr. at 571 (citing Klein, Res. Ex. D at e1144)); however, that category includes amino acid disorders, organic acidemias, urea cycle disorders, fatty acid oxidation disorders, mitochondrial disorders,

[160] Doctor Wiznitzer also noted the authors' statement that their findings with "could be because of chance given the multiple comparison." Klein, Res. Ex. D at e1145.

and glycogen storage diseases (Tr. at 571-72 (citing Klein, Res. Ex. D at e1142, Table 2)). Because of this aggregation, it is unknown to the reader which conditions in the "sickest" category were associated with the increased rates of hospitalization after vaccination. Tr. at 572; *see also* Tr. 575-76. Consequently, "you can't state that this means that children with mitochondrial disorders are at increased risk because they're subsumed within this population." Tr. at 572. Indeed, it is possible that none of the "sickest" children had mitochondrial disorders. *Id.*

Doctor Wiznitzer also pointed out that the researchers urged caution when interpreting their finding "in light of the sparse data with a small number of hospitalizations, the lack of a clear association with any particular vaccine, the long time period over which these hospital events occurred, and the lack of [a] corresponding increase in emergency department visits during the post-vaccine days zero to 14." Tr. at 579-80 (quoting Klein, Res. Ex. D at e1145).

4. Doctor Cederbaum.

In his expert report, Dr. Cederbaum stated that he found no evidence that A.A. "has a mitochondrial disorder that would predispose her to autism when administered the MMR vaccine." Res. Ex. A at 5. In reaching his opinion, Dr. Cederbaum evaluated the asserted temporal relationship between A.A.'s vaccination and the onset of her autistic symptoms; the validity of her mitochondrial disorder diagnosis; and the effectiveness of her prescribed mitochondrial treatment. *Id.*

With regard to the temporal relationship, he observed that the reported proximity of A.A.'s symptoms to her MMR vaccination compressed over time from two to four weeks following vaccination to one to two weeks. Res. Ex. A at 5. He viewed the shortened timeline as the sole product of parental report, unsupported by the medical record. *Id.* Concerning the mitochondrial diagnosis, he found it to be "based on very flimsy evidence that has not been accepted as valid by [those] who work in the area of inborn errors of metabolism and mitochondrial disorders." *Id.* at 6. Indeed, the only support for Dr. Kelley's diagnostic approach was his own work, which consisted of a single published paper. *Id.* (citing Weissman, Pet. Ex. 28).

As for the prescribed treatment, he noted that mitochondrial cocktails are widely viewed as ineffective, albeit harmless. *Id.* at 7 (citing P. Chinnery and L. Bindoff, *116th ENMC international workshop: the treatment of mitochondrial disorders, 14th-16th March 2003, Naarden, The Netherlands*, NEUROMUSCULAR DISORD., 13: 757-64 (2003), filed as Res. Ex. J [hereinafter "Chinnery, Res. Ex. J"]). He stated that it was unclear in this case why Dr. Kelley thought such treatment would make a difference after the damage from the acute insult had already been done. *Id.* at 7-8. In any event, A.A.'s improvement "was not so dramatic as to fairly ascribe it to any intervention." *Id.* at 8. Doctor Cederbaum concluded: "To the majority of the metabolic world, few would even consider a mitochondrial disorder in this setting." *Id.*

At hearing, Dr. Cederbaum reiterated his opinion that A.A. did not have a mitochondrial disease.[161] Tr. at 385, 399-400, 408. He stated that Dr. Kelley's approach to diagnosing mitochondrial disease is not nationally or internationally accepted or established. Tr. at 388. He explained that mitochondrial disease is diagnosed using standardized criteria in the medical literature, including papers published by Walker, Morava, and Bernier.[162] According to Dr. Cederbaum, these standards were established to provide a common language in the field and prevent "intellectual and medical anarchy." Tr. at 386. He stated that the Walker criteria were established for just this reason—"people were calling [everything] mitochondrial disease." Tr. at 386. That problem has now been completely alleviated. Tr. at 386.

Doctor Cederbaum then discussed Pet. Ex. 23B, Dr. Kelley's unpublished method for evaluating and treating patients with autism and mitochondrial disease. Tr. at 387. Doctor Cederbaum stated that the parameters used by Dr. Kelley generally did not meet any of the standard published criteria. Tr. at 387-88. In his view, the paper was "a very permissive and broadly-based and non[-]literature-supported document." Tr. at 388. He did agree with Dr. Kelley that muscle biopsies are unreliable and should not be used as a diagnostic tool. Tr. at 389, 456-57. With regard to Dr. Kelley's reliance on amino acids, Dr. Cederbaum explained that most practitioners would look carefully at alanine levels if they suspected mitochondrial disease, but would not focus solely on amino acids. Tr. at 388. He stated that amino acid levels could be affected by factors other than mitochondrial disease and he "doubted very much whether most people would describe the mitochondria as regulating alanine levels." Tr. at 389-90.

Apart from A.A.'s abnormal alanine level, Dr. Cederbaum did not consider any of the lab results to be indicative of mitochondrial disease.[163] Tr. at 390. He confirmed that plasma alanine is a primary biomarker, but stated that it is "not sufficient, in and of itself, to make the diagnosis." Tr. at 392. In A.A.'s case, the elevated result of 634[164]

[161] Doctor Cederbaum stated that the terms "disease" and "disorder" tend to be used synonymously; however, strictly speaking, disease typically denotes a more serious abnormality or condition than disorder. *See* Tr. at 383, 417-18. He defined "mitochondrial disease" as "an abnormality of the mitochondria that has some demonstrable effect on the function of the mitochondrion." Tr. at 383. He then defined "primary mitochondrial disease" as that caused by a mutation—an inborn mutation—in a mitochondrial gene. Tr. at 382, 418. He explained that the mutation can occur in genes in the nuclear genome, as well as the mitochondrial genome. Mutations in the mitochondrial DNA can result in "heteroplasmy." Tr. at 382. Doctor Cederbaum explained that heteroplasmy occurs when mutations affect some mitochondria and not others, resulting in a "population of normal and abnormal ones." Tr. at 460. "[B]ecause it can vary from tissue to tissue and even from parts of one tissue to another, [there] may [be] variable symptoms or signs in that tissue, depending on the proportion of abnormal mitochondria." Tr. at 460. Primary mitochondrial disease can cause dysfunction ranging from death in the neonatal period to various chronic disorders. Tr. at 383. He defined "secondary mitochondrial disease" as "any effect that does not involve a mutation in a mitochondrial gene but which would appear to affect mitochondrial function." Tr. at 384.

[162] Walker, Res. Ex. T; Morava, Res. Ex. U; Bernier, Res. Ex. V.

[163] His assessment included the labs from Children's Hospital, which he viewed as normal. Tr. at 400.

[164] Doctor Cederbaum slightly misstated the alanine value as 636. Tr. at 392; *see* Pet. Ex. 23A.

would have concerned him; however, he would never have ordered the test that gave that result, because the three previous tests were normal. Tr. at 392. Only if he had seen that elevated result in the beginning would he have repeated the test. Tr. at 392. According to Dr. Cederbaum, the single elevated alanine level was not indicative of mitochondrial disease, but "it would have been worrisome, and [he] certainly would have pursued it further." Tr. at 392.

Doctor Cederbaum stated that he had never heard of glycine as a primary biomarker for mitochondrial disease. Tr. at 393. He noted that it was not discussed in the published literature on the diagnostic criteria for mitochondrial disease, and Dr. Kelley's own paper was yet unpublished.[165] Tr. at 393. In any event, A.A.'s glycine levels were normal. Tr. at 394. As for the purported significance of the alanine and glycine ratio, he confessed that he did not fully understand Dr. Kelley's methods. Tr. at 394. He noted, for example, that it was not standard practice to normalize data as Dr. Kelley had done when investigating for possible mitochondrial disease. Tr. at 394. Nonetheless, he was confident that an elevation in alanine and glycine together would not be sufficient to infer a Complex I deficiency. Tr. at 394-95.[166]

In an effort to demonstrate that various combinations of organic acids have relevance to diagnosing mitochondrial disorders, Dr. Cederbaum was cross-examined regarding the Morgan article (T. Morgan, et al., *Vaccines Are Not Associated With Metabolic Events in Children With Urea Cycle Disorders*, PEDIATRICS, 127: e1147-53 (2012), filed as Res. Ex. C [hereinafter "Morgan, Res. Ex. C"]), which focused on patients with urea cycle disorders. Tr. at 432-38. Specifically, he was asked about "the thinking behind why glutamine, glycine, alanine, arginine, and citrulline" were measured in the study. Tr. at 435. Doctor Cederbaum explained that these amino acids were chosen due to their involvement in the urea cycle and he described the importance of

[165] On cross examination, petitioners' counsel likened Dr. Kelley's unpublished methods for diagnosing mitochondrial disease in children with autism to Dr. Cederbaum's pre-publication discovery of the mitochondrial condition known as MELAS. Tr. at 419-22. In response to questioning, Dr. Cederbaum acknowledged that his work was initially met with some skepticism and that it took a decade for his discovery to gain acceptance. Tr. at 420-21. He stated, however, that unlike Dr. Kelley, he presented the underlying data in public so other researchers could understand, replicate, and build on his conclusions. Tr. at 420. He noted that Dr. Kelley has "held these views about mitochondrial disease [for] 15 years," but still has not disclosed his data. Tr. at 420-21. In response to further questioning, Dr. Cederbaum clarified that he was not criticizing Dr. Kelley's logic, only his conclusions, which are unproven and unaccepted. Tr. at 427-28. He encouraged Dr. Kelley to "publish this and verify it and have it pass through peer review and have it catch on." Tr. at 428. He stated that "it might prove at some time in the future to be correct," it is just "not proven to be correct yet, now." Tr. at 428.

[166] Doctor Cederbaum challenged Dr. Kelley's "observations comparing proven Complex I deficiency and the amino acid levels." Tr. at 395. He stated that a review of the supplementary data in the Weissman paper raised significant concerns in his mind regarding the validity of the conclusions that were drawn. Tr. at 395; *see also* Tr. at 422-24 (cross examination questioning whether Dr. Cederbaum viewed the researchers' institutions as not credible); Tr. at 461-62 (examination by court). Specifically, he examined the data in Supplementary Table 6, which reported the raw data for the muscle biopsies. Tr. at 395. The Complex I levels in some of the data "were so surprisingly low . . . that they were unbelievable in someone who was actually walking around." Tr. at 395-96.

each. Tr. at 435-36. He was then asked whether Dr. Kelley's methods were analogous, as they were likewise based on the measurement of amino acids. Tr. at 436. Doctor Cederbaum appeared to find it difficult to respond to this question, but explained that the comparison was inapt because "glycine is not known to be involved in the respiratory chain." Tr. at 436. It is a respiratory chain disorder (Complex I) problem that Dr. Kelley believed A.A. had.

Doctor Cederbaum was also asked on cross examination to address Dr. Kelley's analogy of proline to hemoglobin A_{1c} in diabetes. Tr. at 437. In diabetes, hemoglobin A_{1c} serves as a biological marker for the average blood sugar levels over a period of about 90 days. *See Hennessey*, 2009 WL 1709053, at*17 (discussing the diagnostic significance of rising hemoglobin A_{1c} levels in diabetes). According to Dr. Kelley, proline levels, when precisely measured, could similarly serve as a marker for increased lactate levels over some unspecified period of time.[167] Doctor Cederbaum responded that he could not elaborate on Dr. Kelley's analogy because it was "not something [he] underst[oo]d or is in the literature." Tr. at 437. Whether "it" referred to hemoglobin A_{1c} or to proline's utility as a biomarker was not clear in Dr. Cederbaum's response. However, it is clear that there is no recognized or accepted crosswalk between proline and ETC function, unlike the widely accepted use of hemoglobin A_{1c} levels to convey average blood sugar levels over recent months.[168]

With regard to the plasma lactate levels, Dr. Cederbaum viewed A.A.'s slightly elevated results as normal. Tr. at 391. Indeed, he and his colleagues would have "ignore[d] even higher values because the frequency of artifact in children[169] is very high and to follow it up is not so easy."[170] Tr. at 391. He stated that lactate is a "very important" biomarker for mitochondrial disease and one he has considered "hundreds of times" in his years of practice.[171] Tr. at 390; *see also* Tr. at 400. He noted, however, that the lactate test is highly susceptible to artifact and is typically ordered only when there is a "reasonable prior probability" of mitochondrial disease. Tr. at 390-91.

Doctor Cederbaum also addressed various other lab results which Dr. Kelley viewed as significant. He stated that A.A.'s CO2 levels were not indicative of

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[167] *See* Tr. at 167-68, 187-88; *see also* Tr. at 667 (court examination).

[168] Because hemoglobin A_{1c} levels are a measurement of blood sugar over a known period of time, diabetic patients no longer need to maintain logs of several-times-daily spot blood sugar testing to show treatment and dietary compliance to their physicians.

[169] He explained that children typically are fearful and struggle when their blood is drawn, which greatly elevates lactate levels, without being indicative of an underlying mitochondrial problem. Tr. at 391-92.

[170] Doctor Cederbaum noted that a routine and reliable alternative would be to "collect the lactate and pyruvate [together] . . . under conditions that we would call rest. And we have a specific protocol for doing that." Tr. at 391.

[171] He was surprised that Drs. Kelley and Zimmerman "dismissed the lactate as being unimportant when it's one of the primary biomarkers for mitochondrial disease." Tr. at 393.

mitochondrial disease. Tr. at 396. Indeed, according to Dr. Cederbaum, CO2 levels are not a primary biomarker for mitochondrial disease or "even a primary biomarker for metabolic disease in general." Tr. at 396. Similarly, creatine kinase is not a primary biomarker for mitochondrial disease. Tr. at 397. He also stated that he was not aware of any peer-reviewed literature that identified AST or the AST-ALT ratio as a primary marker for mitochondrial disease in the general population. Tr. at 398-99. Doctor Cederbaum stated that he was open-minded toward the idea that the AST-ALT ratio or creatine levels could be valid criterion for at least suspecting mitochondrial disorder, however, they are not presently criteria published in the medical literature. Tr. at 398-99. He would not accept them as diagnostic of mitochondrial disorder. Tr. at 398-99. I note that this testimony was effectively unrebutted, as no peer-reviewed literature filed identified these tests as primary biomarkers for mitochondrial disease. In his view, none of A.A.'s lab results were indicative of a likely Complex I deficiency. Tr. at 400-01.

In response to additional questioning, Dr. Cederbaum stated that he had not previously heard that a reaction to L-carnitine could be a diagnostic indicator of a Complex I deficiency.[172] Tr. at 401. He stated that the basis for Dr. Kelley's assertion that L-carnitine activates Complex I was not apparent. Tr. at 401. As for the use of vitamin cocktails, Dr. Cederbaum stated that he does not view them as an effective treatment.[173] Tr. at 403. He acknowledged that Dr. Zimmerman and Mr. Allen described apparent temporally related improvement; however, a cause and effect relationship has not been shown. Tr. at 404.

Doctor Cederbaum also indicated that mitochondrial PDD or mitochondrial autism was not an established diagnosis in the metabolic community, but noted that a "cohort of individuals" around the country believe it is valid. Tr. at 404. The majority of the community does not view it as a legitimate diagnosis, however, especially in light of newer techniques, such as "whole exome sequencing, that have found presumed mutations in autism, [which] don't include mitochondrial genes, but they do include

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[172] In response to my questioning, Dr. Cederbaum stated that carnitine is not known to cause seizures; thus, in his view, the relationship between A.A.'s treatment with carnitine and her seizures is solely a temporal one. Tr. at 465.

[173] On cross examination, Dr. Cederbaum reiterated that this "type of treatment . . . has been used for years, [but] there's no compelling evidence it really works." Tr. at 459 (citing Chinnery, Res. Ex. J); *see also* Tr. at 459-60 (citing S. Yazdani, et al. eds, CHRONIC COMPLEX DISEASES OF CHILDHOOD: A PRACTICAL GUIDE FOR CLINICIANS (2011), filed as Pet. Ex. 74 [hereinafter "Yazdani, Pet. Ex. 74"], at 185). I queried Dr. Cederbaum about why vitamin cocktails would be used if there is no evidence that it works. Tr. at 462-64. In his view:

> [P]hysicians have a very low tolerance for being able to say, 'I do nothing.' So, there's this suspicion that vitamins can't possibly be harmful, and . . . you can develop a rationale for why a cocktail of these substances might work, and you throw in carnitine, which has a lesser rationale; you throw in thiamine, which we know most affects the pyruvate dehydrogenation and not the mitochondria; you throw in riboflavin because it's a cofactor for Complex II; Co-Q is an electron transporter, and it may be if you throw in Co-Q, you'll bypass a block."

Tr. at 462.

genes that have to do with brain development and synaptic formation." Tr. at 404. He noted that such testing was not available in 2002. Tr. at 405-06. Genetic testing for mitochondrial disease was not performed on A.A. Tr. at 406.

On cross examination, Dr. Cederbaum agreed that a person with a mitochondrial disorder could display signs and symptoms of autism. Tr. at 418. In his view, autism is "a symptom complex . . . caused by a lot of different things." Tr. at 418. As such, he found no inherent reason why "you couldn't have some [mitochondrial] patients who display that symptom complex." Tr. at 418.

Doctor Cederbaum discussed A.A.'s treatment with valproate (Depakote). Tr. at 406-08; *see also* Tr. at 438-46 (cross). He stated that valproate is "absolutely not" recommended for patients with mitochondrial disease, because it has "been known for many years . . . [as] a mitochondrial toxin." Tr. at 406. He explained that a physician "would never use it" if he or she suspected mitochondrial disease. Tr. at 406. He stated that if A.A. had a mitochondrial disease he would have expected to see an elevation of lactate and pyruvate, as well as a physical reaction to Depakote. Tr. at 407-08. He referenced several medical articles[174] that reported "severely abnormal reactions to valproate [Depakote], sometimes when they knew that it was a mitochondrial disease and used it inadvertently or ignorantly, and sometimes [when] the suspicion of mitochondrial disease was not raised until [after the] horrible reaction." Tr. at 406. Given this contraindication, Dr. Cederbaum questioned why A.A.'s physicians would prescribe Depakote to treat her seizures, which were not severe, when "there's a whole pharmacopeia of available anticonvulsants." Tr. at 408; *see also* Tr. at 440-41 (cross). In his opinion, they were "either woefully ignorant or they didn't believe that [she had] a mitochondrial disorder in the first place." Tr. at 408.

In response to questioning on cross examination, Dr. Cederbaum stated that it was possible that some mitochondrial disorders would be permissive of valproate. Tr. at 440. However, the current standard of care is to avoid the drug unless the patient has a "desperate, desperate, intractable seizure disorder." Tr. at 441. A.A. did not have a severe, untreatable seizure disorder. Tr. at 440. Doctor Cederbaum was asked to confirm that valproate had not worsened A.A.'s mitochondrial dysfunction. Tr. at 441. He responded that that was true "because she didn't have a mitochondrial disorder. Tr.

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[174] J. Uusimaa, et al., *Prospective study of* POLG *mutations presenting in children with intractable epilepsy—prevalence and clinical features*, EPILEPSIA, 54 (6): 1002-11 (2013), filed as Res. Ex. W [hereinafter "Uusimaa, Res. Ex. W"]; R. Saneto, et al., POLG *DNA testing as an emerging standard of care before instituting valproic acid therapy for pediatric seizure disorders*, SEIZURE, 19: 140-46 (2010), filed as Res. Ex. X [hereinafter "Saneto, Res. Ex. X"]; J. Stewart, et al., *Polymerase γ Gene* POLG *Determines the Risk of Sodium Valproate-Induced Liver Toxicity*, HEPATOLOGY, 52 (5): 1791-96 (2010), filed as Res. Ex. Y [hereinafter "Stewart, Res. Ex. Y"]; E. De Greef, et al., *Mitochondrial Respiratory Chain Hepatopathies: Role of Liver Transplantation. A Case Series of Five Patients*, JIMD REPORTS, 4: 5-11 (2011), filed as Res. Ex. Z [hereinafter "De Greef, Res. Ex. Z"]; A. Mindikoglu, et al., *Valporic Acid-Associated Acute Liver Failure in Children: Case Report and Analysis of Liver Transplantation Outcomes in the United States*, PEDIATR., 158: 802-07 (2011), filed as Res. Ex. AA [hereinafter "Mindikoglu, Res. Ex. AA"].

at 441. He elaborated that her condition did not "get materially worse" and her irritability could not be ascribed "one way or another to a mitochondrial condition." Tr. at 441. He also confirmed that, based on her AST levels, the drug did not affect her liver function. Tr. at 441-46.

Doctor Cederbaum was asked to address possible and known stressors in mitochondrial disease. Tr. at 409. He explained that "[a]ll inborn errors have stressors that appear to exacerbate them," although many remain unidentified. Tr. at 409. He stated that intercurrent illnesses, such as respiratory infection or a urinary tract infection, are known stressors of mitochondrial disease. Tr. at 410. As for vaccines, he stated that they are not known stressors, but "are always given with caution." Tr. at 411-13 (citing Morgan, Res. Ex. C; Klein, Res. Ex. D).

On cross examination, Dr. Cederbaum reiterated that infections are known metabolic stressors. Tr. at 429. He also acknowledged that metabolic decompensation has been reported following immunization. Tr. at 429-30, 456. Asked whether he saw "any correlation between infections and what happens after an immunization," he responded that there is "an inflammatory component to both, [but] we have not yet in medicine defined [that] inflammatory component . . . that might in some instances cause a metabolic deterioration." Tr. at 430. Concerning the putative "window of vulnerability" discussed by Dr. Kelley, he noted that Dr. Kelley's window of vulnerability "occurs when we know that the onset of autism is most common. So, it could be just cotemporal"—"they are not necessarily related as cause and effect." Tr. at 431.

Doctor Cederbaum addressed several research articles submitted by Dr. Zimmerman pertaining to mitochondrial dysfunction and autism. Tr. at 413-16 (citing Tang, Pet. Ex. 65; Anitha, Pet. Ex. 66; Ginsberg, Pet. Ex. 67; D. Rossignol and R. Frye, *Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis*, MOLEC. PSYCHIAT., 17: 290-314 (2012), filed as Pet. Ex. 68 [hereinafter "Rossingnol, Pet. Ex. 68"]; Chauhan, Pet. Ex. 69). Doctor Cederbaum stated that he had read the articles, but viewed them as uninformative because petitioners' stated hypothesis relates to "a primary genetic abnormality," whereas the data in the articles relates to "a secondary abnormality"—it is "apples and oranges." Tr. at 416. In his opinion, the data from the articles simply "are not interpretable or applicable at this time to this case." Tr. at 416.

On cross examination, Dr. Cederbaum was asked about the Walker (Res. Ex. T), Morava (Res. Ex. U), and Bernier (Res. Ex. V) articles, which discuss diagnostic criteria for mitochondrial disorders. Tr. at 446-47. In response to questioning, Dr. Cederbaum confirmed that the Walker criteria were developed for adults, but noted that it was later expanded by Morava and Bernier. Tr. at 446-47. He acknowledged that the criteria outlined in the papers were propositional at the time; however, he indicated that there is now general acceptance of the criteria as applicable to both patient populations. Tr. at 448-49. There are practitioners, though, such as Dr. Kelley, who "fe[el] no compunction about applying [their] own criteria," so acceptance is not universal. Tr. at 449. When asked to clarify what he meant by Dr. Kelley's own criteria, he responded the "ones that

alanine and glycine elevation alone, with creatine kinase and AST-ALT ratio are sufficient to diagnose a mild form of [mitochondrial disorder]." Tr. at 449.

On cross examination, Dr. Cederbaum elaborated on the various criteria discussed in the articles. Tr. at 449. As an initial matter, he noted that the articles were written for the population that studies this area, so they sometimes are "almost like a shorthand"—the authors assume those reading the article have a basic familiarity with the concepts and theories underlying the research. Tr. at 450. So "[w]hen you talk about metabolic abnormalities, lactate, pyruvate, and alanine are understood as being a criterion." Tr. at 450-51. Doctor Cederbaum was then questioned about alanine as a substitute marker for pyruvate. He responded that alanine was "absolutely not" a substitute, but "a reflection of pyruvate." Tr. at 451. He continued that "nobody would suggest that it's a substitute. In fact, alanine can be elevated in circumstances in which pyruvate is normal." Tr. at 451. As an example, he explained that

> in pyruvate dehydrogenase deficiency, where there is no oxidative problem, the lactate-pyruvate ratio is normal as it would be in someone without any metabolic disorder, whereas generally, in mitochondrial disorders, where there's an oxidative problem, you may have elevated alanine, but the lactate-pyruvate ratio will be distorted in favor of lactate, because of the oxidation.

Tr. at 451-52; *see also* S. Yazdani, et al. eds, CHRONIC COMPLEX DISEASES OF CHILDHOOD: A PRACTICAL GUIDE FOR CLINICIANS (2011), filed as Pet. Ex. 74 [hereinafter "Yazdani, Pet. Ex. 74"] (textbook chapters Dr. Cederbaum wrote on disorders of pyruvate metabolism and pyruvate dehydrogenase deficiency). He also confirmed that "you [can] have a normal lactate and pyruvate level and still have a mitochondrial problem." Tr. at 453.

In response to additional questioning on cross examination about his textbook chapters, Dr. Cederbaum agreed that there were a wide range of symptoms that can appear in a mitochondrial disorder. Tr. at 455 (citing Yazdani, Pet. Ex. 74). He also agreed that both single and multisystem organs can be affected in a respiratory chain disorder. Tr. at 455. He confirmed that the onset of symptoms in the multisystem disorder can appear at different times—for example, the brain symptoms could appear before the gastrointestinal symptoms. Tr. at 456.

Doctor Cederbaum was cross-examined regarding the use of ratios for comparing biochemical markers in metabolic research. Tr. at 454. He confirmed that their use is "perfectly reasonable" and, when valid, can help researchers identify and correct false positives in test results. Tr. at 454. Doctor Cederbaum acknowledged that Dr. Kelley's use of ratios was done for this reason; however, he did not indicate whether he believed the ratios to be valid. Tr. at 455.

On cross examination, petitioners' counsel recalled that Dr. Cederbaum agreed with Dr. Kelley that muscle biopsies are unreliable and should not be used as a

diagnostic tool. Tr. at 457. She then noted that muscle biopsy results were classified as one of the major criteria in Walker and asked Dr. Cederbaum what criterion has taken its place. Tr. at 457 (citing Walker, Res. Ex. T at 264). He responded that the substitute criterion "would be persistent, really unequivocal elevations in lactate, and a multisystem disease." Tr. at 457. He noted, however, that "the bar" has really been "raised by the newer technologies. So that now there's no way to diagnose a mitochondrial disorder without doing whole exome [analysis], which will look at both the mitochondrial genome and the nuclear genome." Tr. at 457.

At the conclusion of his testimony, I asked Dr. Cederbaum if in summary it would be correct to say that he did not view Dr. Kelley's hypotheses as wrong, just not proven. Tr. at 466. He affirmed my statement. Tr. at 466. I then asked him whether by "not proven" he meant "not probable or not certain or just that we don't know." Tr. at 466. Doctor Cederbaum responded that when a scientist proposes something, the onus is on that person "to demonstrate or prove . . . the veracity of what they're proposing." Tr. at 466. With regard to Dr. Kelley's hypotheses, "there is a way of doing that now, and that would be whole exome [analysis]." Tr. at 466. He stated that Dr. Kelley "ought to be figuring out a way to pay for whole exome sequencing" to determine whether any of his patients have mitochondrial gene mutations. Tr. at 466. Doctor Cederbaum recognized that a patient could have a mitochondrial disorder and also have normal exome results, with no abnormality in a mitochondrial gene; however, he reiterated that the onus is on Dr. Kelley to show "that some of these patients have a mitochondrial gene that's mutated." Tr. at 466-67. Such findings would allow a reasonable inference that some others might have mutations as well. Tr. at 466-67.

Doctor Cederbaum also emphasized the importance of publication and reproducibility. Tr. at 467-68. He explained that publication exposes an idea to a knowledgeable community and allows them to review and pass judgment on it. Tr. at 467. Publication generally represents acceptance by scientific peers. Tr. at 467. Although "correct ideas may [initially] get rejected, . . . they won't get rejected always, and you can get anything published today," especially with so many options available. Tr. at 467.

Doctor Cederbaum also explained that reproducibility—the ability of others to duplicate the results—factors into whether an idea is considered proven or established. Tr. at 467-68. He explained, for example, that a paper on Dr. Kelley's theory would provide the "biochemical data alongside whole exome data, and maybe because it's autism, [there would be] a comparative genome hybridization." Tr. at 468. This would allow "someone else [to] take their series of patients and replicate it"—they would try to repeat what Dr. Kelley says he has done. Tr. at 468. Unfortunately, in its current form, Dr. Kelley's methods and theories cannot be replicated or confirmed. Tr. at 468.

VII. Factual Findings.

I have carefully considered the record as a whole in arriving at the factual findings set forth below.

A. Pre-Vaccination.

1. Pre-Vaccination Health.

During her first 15 months of life, A.A. suffered multiple minor illnesses, including respiratory infections, conjunctivitis, and OM. She was physically normal upon examination at each of her well child visits through 12 months of age. She also was physically normal at her 15-month visit, except for fluid-filled tympanic membranes indicative of an ear infection. A.A. suffered from chronic ear infections.

2. Pre-Vaccination Development.

A.A. had symptoms of ASD prior to the administration of the October 23, 2000 MMR vaccination. Although she developed normally during her first year of life and achieved expected milestones, by 15 months of age A.A. had possessed few if any functional words. Although the Denver II reflected three words, the video evidence suggested a very limited vocabulary.

I do not accept the testimony of A.A.'s father and aunt that she possessed between 12 and 100 words by 15 months of age, or that she had the ability to name colors, count, or tell "knock-knock" jokes.[175] Their statements are contrary to more reliable contemporaneous evidence, including earlier parental reports and video taken during the period in question.

Petitioners provided histories closer in time to the described events (and before they began to blame the MMR vaccine for A.A.'s problems), which indicated that A.A. spoke very few words by 15 months of age and primarily made animal, and other oral sounds, which lacked meaning.[176] These reports were confirmed by the video evidence recorded on October 14, 2000, wherein she vocalized but spoke no words, including "ma-ma" and "da-da."[177]

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[175] I credit Dr. Wiznitzer's testimony that it would be "highly, highly unlikely" for a child that age to have such a vocabulary due to the way language develops and also "the immaturity of the oral motor mechanism in terms of verbalization." Tr. at 535-36 (cross). In his many years of practice he could not recall ever meeting a child who had 24 words at 15 months of age—"functional words that they use independently." Tr. at 536. Even Dr. Zimmerman conceded that A.A.'s reported ability to name colors was probably overstated based on the level of development he saw on the video. Tr. at 357-59.

[176] *See, e.g.*, Pet. Ex. 5, p. 5 (parental report at speech and language evaluation on September 5, 2001, that A.A. spoke "her first word 'Quack' at 1 year and [spoke] a little more/using animal sounds at 15 months"); Pet. Ex. 9, p. 96 (parental report to Dr. Lavenstein on September 16, 2001, that A.A. "had some oral sounds" in October 2000, "but then subsequently regressed"); Pet. Ex. 6, p. 25 (parental report to Dr. Raymond on February 13, 2002, that prior to approximately 16 months of age, she "was able to make 'animal sounds' such as 'roar!' when asked, and was able to state her age").

[177] With regard to A.A.'s language development as seen in the video, Dr. Zimmerman—petitioners' own expert—testified that she was "not forming words," but "making word sounds." Tr. at 297-98. In later testimony, he recalled her "babbling some word sounds" during the video, but no other specific words. Tr.

A.A. also exhibited abnormal behavior for a 15 month old child. In the October 14 video, A.A. demonstrated normal gross motor skills and an appropriate interest in her surroundings; however, the quality and level of her interpersonal interactions with her parents was diminished. As Dr. Wiznitzer observed, she did not seek to be picked up and held by her parents and made limited eye contact.[178] She also engaged in hand flapping—a stereotypy commonly seen in autistic individuals.[179]

According to Dr. Zimmerman, A.A.'s behavior appeared normal in "all respects" and he specifically disagreed with Dr. Wiznitzer that she exhibited any hand flapping during the video.[180] Although he did note other repetitive movements, he explained them away, stating that abnormal motor behaviors and stereotypies almost always come after loss of language and relatedness—there is a "hierarchy of symptoms" in ASD.[181] Later, however, he stated that stereotypies can come before loss of language, especially in a child who develops autism early.[182] But he maintained that A.A. was not such a child because "her development was normal" and the behaviors were simply the "immature movements" of a young child.[183]

I find Dr. Wiznitzer's testimony more persuasive on the nature of AA's behavior on the videos, particularly in view of his clinical experience. Although both pediatric neurologists were well-qualified to opine on ASD, it appears to me that Dr. Zimmerman's focus in research has been on biochemical and cellular differences between those with ASD and those with typical development, whereas Dr. Wiznitzer's focus has been on ASD behaviors, co-morbidities, and diagnosis. *See* Pet. Ex. 26, pp. 16-24 (Dr. Zimmerman's publications) and Res. Ex. L, pp. 13-23 (Dr. Wiznitzer's publications). Doctor Wiznitzer's testimony tracked what I observed on the videos.

B. Post-Vaccination Health.

1. Health.

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at 344 (cross). Even if one accepts that "moo" is a functional word, as Dr. Zimmerman contended, A.A. still had fewer words than would be expected for a 15 month old child. *See* Tr. at 677.

[178] Although Dr. Zimmerman commented that A.A. appeared to be "making eye contact with the person who's taking the film," he conceded that he could not know whether she was making eye contact with her parents or simply looking at the camera. Tr. at 345 (cross).

[179] Doctor Zimmerman later observed this behavior first-hand during an early follow-up visit on July 15, 2002. *See* Pet. Ex. 6, p. 21.

[180] Tr. at 299.

[181] Tr. at 676-77.

[182] Tr. at 681.

[183] Tr. at 681-82.

A.A.'s first medical visit following her MMR vaccination was on December 18, 2000, when she was approximately 17 months old. She was treated for a viral infection and early OM.

Prior to that visit, she was not seen or otherwise treated for any illness or medical concern—a nearly two-month period after the MMR vaccination.

I find that A.A. was not ill as the result of her MMR vaccination. I do not accept Mr. Allen's testimony that A.A. developed a fever on the night of October 29, 2000, or that he or his wife called A.A.'s pediatrician seeking advice. There is no record of the fever or of the telephone call. A spiking fever, which reportedly lasted four days, would likely have been noted somewhere by her pediatrician—especially if they called twice, as asserted.[184]

Petitioners had previously consulted a pediatrician in person when A.A. was ill. It is counter-intuitive that that would not have done so when she spiked a fever lasting four days. It was petitioners' custom to take A.A. in for office examinations whenever she was sick, regardless of symptoms. As such, it is very unlikely that petitioners would simply have called the pediatrician in this instance.[185]

As was the case prior to her vaccination, A.A. suffered from chronic OM. The medical records reflect that between her first post-vaccination appointment on December 18, 2000, and her two-year well child visit on August 6, 2001, she was diagnosed with five ear infections. Other illnesses during this period included viral infection, URI, and UTI.

2. Developmental Regression

A.A. did not experience an abrupt deterioration of her development after the MMR vaccination. Based on contemporaneous medical records, nearly two months elapsed before she returned to her pediatrician (December 18, 2000), and even then nothing was observed or reported as to a loss of skills or other significant behavioral change.

The first report of any developmental concern was more than four months after the MMR vaccination, on March 1, 2001, when A.A. was seen for her 18-month well child visit.[186] At that visit, her health care provider noted that she had not achieved

[184] *See* Tr. at 79-80.

[185] Petitioners took A.A. to the pediatrician for the same symptoms—high fever, irritability, and refusal to eat—on November 11, 1999, at four months of age. They were instructed at that visit about the seriousness of a fever exceeding 100 degrees and of symptoms lasting more than three days. *See* Pet. Ex. 9, p. 62.

[186] As previously noted, A.A. was more than 19 months old at the time of the visit.

some of the expected milestones, and her mother expressed concern about her language skills and withdrawing behavior. Her concern about A.A.'s social and language development had likely grown over time, as A.A.'s mother did not mention any abrupt deterioration or point at which her concern crystalized, and did indicate that there had been a problem (attributed to the prior nanny) over several months, and that A.A, was opening up more with the new nanny. A.A. had 4-10 words (the Denver II chart at Pet. Ex. 9, p. 7 reflected 6 or more words) at this visit, suggesting an increase in vocabulary, although there was a concern about consistency in her language.

Over the next few months, A.A. returned to the doctor for various illnesses, including a series of ear infections. On May 7, 2001, her pediatrician formally assessed her with delayed speech. The diagnosis was repeated at her two-year well child visit on August 6, 2001, and she was referred for speech evaluation.

At the speech evaluation, which took place on September 5, 2001, petitioners reported that A.A. "stopped speaking after having 3 ear infections in a row"[187]—the last of which occurred nearly six months after vaccination.

Although Mr. Allen testified to an alternate, condensed timeline, supported by the testimony of Ms. Edick, involving abrupt changes in A.A.'s behavior within one to two weeks of her MMR vaccination, including loss of language, flattened emotions, decreased eye contact, and diminished social interactions, I do not credit their testimony. I am certain that these changes occurred, as they were noted in later evaluations, but I do not find it probable that they occurred abruptly within a few weeks of the MMR vaccination.

Rather, I find it likely that A.A.'s behavioral problems began to be more noticeable as she got older. The Christmas 2000 video showed behavioral differences suggestive of ASD, but to her parents, they likely represented toddler obstinacy and tantrums. Certainly, they were not mentioned at the March well-child visit or in the several histories provided before Mr. Allen's internet research prior to a call to Countryside in mid-January 2002.

Doctor Zimmerman testified that he observed behavioral changes between the October 14 and October 29 videos that correlated with Mr. Allen's report that A.A. "changed within one to two weeks after the MMR immunization."[188] He stated that the rapidity of A.A.'s regression was "striking" and "somewhat unusual."[189] In response to questioning he discussed the role of environment on behavior and recognized that the videos were shot in different settings;[190] however, he did not think that was a factor in

[187] Pet. Ex. 5, p. 5.

[188] Tr. at 302-03.

[189] Tr. at 349.

[190] Tr. at 355-56.

this case.[191] He also acknowledged that the abnormal behavior he identified in the video (*e.g.*, lack of expression, diminished interest) could have been due to the illness that was reflected in the medical records from her 15-month visit.[192]

Doctor Wiznitzer, on the other hand, saw no evidence of a rapid regression or any significant behavioral changes.[193] He elaborated that A.A.'s behavior at the pumpkin patch on October 14 was strikingly similar to her behavior at the Halloween party on October 29.[194] He also explained that any perceived differences in A.A.'s behavior while at home on October 14 as compared to that at the Halloween party were largely attributable to her age and personality and not evidence of a major change.[195] He stated that what was important from a developmental perspective was her evident awareness of her surroundings and of the people around her.[196] My own observations and conclusions are in accord with Dr. Wiznitzer's.

Both experts agreed that by Christmastime A.A.'s behavior was clearly abnormal—she did not vocalize, had diminished social interaction, and engaged in inappropriate play.[197] However, their opinions differed as to whether the behavior was a continuum of deterioration from that seen in later October.[198] In Dr. Zimmerman's view, "her condition five days after [vaccination] appeared to persist."[199] Doctor Wiznitzer indicated that there was insufficient evidence to find that the behaviors were a progression.[200]

In view of all of the evidence of record, I do not find the testimony offered by Mr. Allen and Ms. Edick with respect to the timeline of A.A.'s developmental deterioration to

[191] Tr. at 679.

[192] Tr. at 353-54; *see also* Tr. at 301 (Doctor Zimmerman commenting that in the October 29 video, A.A. looked as though she did not feel well).

[193] Tr. at 493, 495.

[194] Tr. at 495; *see also* Tr. at 493 (explaining that he focused on those segments due to the similarity of the environment).

[195] Tr. at 490 (noting a "clear difference" between her behavior and social interactions when she was at home as compared to outside in public, but attributing it to stranger anxiety and shyness).

[196] Tr. at 494-95.

[197] Tr. at 303 (Dr. Zimmerman); 541-42, 605-08 (Dr. Wiznitzer).

[198] Tr. at 303-04 (Dr. Zimmerman); 608 (Dr. Wiznitzer).

[199] Tr. at 303-04.

[200] Tr. at 608.

be reliable. I do not question their honesty;[201] I do question their recall. This was a family with easy access to health care, with a nanny who could take A.A. to the doctor when her parents were working. Despite the extremely concerning changes described,[202] petitioners did not contact A.A.'s doctor or voice concern to any other medical professional.[203] And when she was treated on December 18 for a viral infection and early OM, these troubling developments went unmentioned. This makes no sense.

As I noted above, petitioners were consistent in taking A.A. to the doctor when she was sick, including for very minor illnesses. That they would not have reached out to A.A.'s pediatrician in these circumstances is inexplicable. Indeed, I note that even after Mr. Allen began blaming the MMR vaccination for A.A.'s problems, the timeline between vaccination and onset was different. He reported to A.A.'s physician in early 2002: "Her behavior started 30 days post MMR."[204]

I emphasize that I have a great deal of respect for Dr. Zimmerman as a physician and expert. However, I think his view of the events post-vaccination were based on and shaped by the history he was provided at the initial visit. The history of a rapid regression, one he thought atypical of ASD, meshed with his research interest in mitochondrial disorders and ASD. He ordered testing, and eventually treatment. Letting go of the basis for this course of events could be difficult. However, setting aside the history he had been provided, when he was asked to identify medical evidence showing developmental abnormalities or changed behavior shortly after vaccination, he could not do so.[205] Doctor Zimmerman also stated that if he were to base his opinion only on the October 14 and December 25 videos, without regard to the October 29 video, he would not characterize the behavioral changes he observed as rapid.[206] I asked him that question because of the testimony of Dr. Wiznitzer and my own observations that A.A.'s behavior at the pumpkin patch looked a lot like her behavior at the Halloween parade and party.

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[201] The only area in which I question Mr. Allen's honesty is in the claim than no other videos of A.A. existed, particularly in view of his testimony that he filmed her frequently.

[202] *See* Tr. at 119 (Ms. Edick stated that the behavior she saw on Veterans Day weekend "really affected [her]." She could not remember saying anything about her concerns to the petitioners; however, she did recall discussing it with her own parents.). This, too, is inexplicable. As close as the family apparently was, and given Ms. Edick's training in special education, I find it very difficult to accept that she would not—gently—have mentioned that some of A.A.'s behaviors should be discussed with her pediatrician. Given petitioners' response to the speech therapist's suggestion that she might have ASD (she saw an ASD specialist at Children's Hospital in Washington, DC just 11 days later) I cannot imagine that they would not have responded equally quickly to a suggestion or observation that A.A.'s behaviors were not normal.

[203] *See* Tr. at 81-82; *see also* Tr. at 45 (In retrospect, Mr. Allen wished that he had called the doctor, but stated that he was not sure what he would have said.).

[204] Pet. Ex. 9, p. 35.

[205] Tr. at 348.

[206] Tr. at 353 ("Three months would not be rapid, no.").

Instead, I credit Dr. Wiznitzer's opinion, as it is consistent with the contemporaneous medical records. Doctor Wiznitzer persuasively explained that A.A. had early signs of autism prior to vaccination[207] and that her subsequent autistic presentation was not atypical.[208] He testified that autism usually manifests between age one and two years, but symptoms are always present before age three.[209] He also testified that autistic regression is not an abrupt occurrence;[210] instead, language and social skills are lost over a period of weeks to months.[211] In his view, A.A's autistic presentation followed this course, beginning with delayed speech prior to vaccination and continuing with a gradual deterioration of social skills and other behaviors.[212] Her eventual ASD diagnosis was fully supported by the medical records.[213]

C. Diagnosis of Mitochondrial Disease, Disorder, or Dysfunction.

The preponderant evidence does not support a finding that A.A. has or had a mitochondrial disease, disorder, or dysfunction. Doctor Kelley's diagnosis was not made using established criteria, but an unpublished method that has not been peer-reviewed, adopted by other laboratories, or recognized as a valid diagnostic approach by the mitochondrial community at large.[214] Indeed, Dr. Kelley himself stated that A.A. would not meet the criteria for a mitochondrial diagnosis using established criteria.[215]

Early in his treatment, Dr. Zimmerman suspected that A.A. "might have mitochondrial problems."[216] The basis for this belief was her "apparently rapid deterioration following her MMR vaccin[ation]"—a pattern he claimed he had seen in other children with mitochondrial problems.[217]

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[207] Tr. at 500-01.

[208] Tr. at 500.

[209] Tr. at 497.

[210] Tr. at 597-602 (also commenting that "an overnight story" would lead him to "start looking for other disorders").

[211] Tr. at 600-01.

[212] Tr. at 500 (also stating that even "a relatively rapid regression" would still be "within the framework of what's been described for the population").

[213] Tr. at 499.

[214] Tr. at 388 (Dr. Cederbaum)

[215] Tr. at 252.

[216] Tr. at 306-07.

[217] Tr. at 307. One of the difficulties with this correlation is that regression in autism is not infrequent. *See Dwyer*, 2010 WL 892250, at *37-40; *Synder*, 2009 WL 332044, at *39-42; *see e.g., Dwyer*, 2010 WL

I accept and acknowledge that Drs. Kelley and Zimmerman were treating physicians. Their decision to treat A.A. based on the diagnosis of "mitochondrial autism" that they reached certainly attests to their belief in the diagnosis. Their belief that she improved on such treatment is more difficult to assess and credit, as they acknowledged her positive response could not be separated from the effect of other therapies she was concurrently receiving. And, to the extent that her improvement was based on subjective assessments, I note that petitioners thought A.A. improved on chelation therapy, too, which was designed to remove heavy metals, not treat mitochondrial problems.

Genetic testing for mitochondrial defects was negative. That is not uncommon, even in children with symptoms meeting the mainstream diagnostic criteria. With the exception of one high alanine level on testing ordered in 2003 (after three earlier tests for alanine were normal), A.A. had none of the classic markers for mitochondrial disease. Although Drs. Zimmerman and Kelley thought there was a history of a sudden regression post MMR vaccination, based solely on parental histories, I have found that there was no sudden regression.

Essentially, the "mitochondrial autism" diagnosis rests on the unpublished research of Dr. Kelley and the anecdotal observations of Dr. Zimmerman. And, Dr. Kelley's opinion is, in essence, based on his re-evaluation and "normalization" of the findings of one outside laboratory, which reported A.A.'s results as normal, and on the test results from his own laboratory, which he acknowledged were not accepted by the mitochondrial disease community at large.

At hearing, Dr. Kelley testified at length about his diagnostic approach, but was unable to cogently explain his method, which involved opaque calculations,[218] obscure protocols,[219] and data accessible only to him.[220] Although he borrowed some elements

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892250, at *63-77; *Snyder*, 2009 WL 332044, at *142-47; C. Johnson, et al., *Identification and Evaluation of Children With Autism Spectrum Disorder*, PEDIATRICS 120(5): 1183-1215 (2007), filed as Res. Ex. M ["Johnson, Res. Ex. M"], at 1192. The MMR vaccination is commonly given at 12-15 months of age, a time frame when ASD symptoms often emerge. When anecdotal data connecting regression to the MMR is cited, it is difficult to determine if the correlation is suggestive of causation or merely coincidental. This problem with Dr. Zimmerman's data was discussed by Dr. Wiznitzer in his testimony, including references to the epidemiologic studies on which he relied. The epidemiology was also extensively discussed in the Theory 1 OAP decisions. *See, e.g.,Snyder*, 2009 WL 332044, at *142-47; *see also* Johnson, Res. Ex. M at 1184-86.

[218] *See, e.g.*, Tr. at 159-60; 165-67; 635-45 (normalized ratios to mean values).

[219] *See, e.g.*, Tr. at 162, 164 (four-hour fasting blood sample).

[220] *See, e.g.*, Tr. at 167; 654-55 (underlying data for certain values not disclosed or publicly available).

of published diagnostic criteria,[221] other aspects of his analysis were of his own design,[222] without support.[223]

Doctor Wiznitzer expressed significant concerns with Dr. Kelley's "very unclear" diagnostic methodology.[224] In particular, he questioned the validity of certain calculated values, the acceptance of unusually high standard deviations, and the application of normal range values to test results from other labs.[225] He viewed Dr. Kelley's data and calculations with extreme reservation—indeed, he found it difficult to "state that th[e] information ha[d] any value."[226]

Doctor Cederbaum testified that A.A.'s mitochondrial diagnosis was "based on very flimsy evidence that has not been accepted as valid by [those] who work in the area of inborn errors of metabolism and mitochondrial disorders."[227] He stated that Dr. Kelley's approach to diagnosing mitochondrial disease is not nationally or internationally accepted or established.[228] Mitochondrial conditions are diagnosed using standardized criteria in the medical literature, including papers published by Walker, Morava, Bernier.[229] He explained that such standards were established to provide a common language in the field and to prevent misdiagnosis because "people were calling [everything] mitochondrial disease."[230] He stated that the only support for Dr. Kelley's diagnostic method was his own work, which consisted of a single published paper, and that paper did not stand for the proposition for which he cited it.[231]

Doctor Cedarbaum also noted that vitamin cocktails are widely viewed as ineffective, and that treatment with such could not be fairly cited to as having improved

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[221] *See, e.g.*, Tr. at 159-60 (discussing the common practice of using ratios to evaluate the levels of certain amino acids).

[222] Tr. at 159 (stating that his method of analysis was "an elaboration on what many people do"—only taken "a couple steps further").

[223] *See, e.g.*, Tr. at 451 (Doctor Cederbaum stating that alanine was "absolutely not" a substitute marker for pyruvate, and "nobody would suggest that it's a substitute").

[224] Tr. at 510.

[225] Tr. at 510-15

[226] Tr. at 515.

[227] Res. Ex. A at 6.

[228] Tr. at 388.

[229] Tr. at 385-86.

[230] Tr. at 386.

[231] Res. Ex. A at 6 (citing Weissman, Pet. Ex. 28).

A.A.'s condition.[232] According to Dr. Cederbaum, few in the metabolic world "would even consider a mitochondrial disorder in this setting."[233] Because there are no real side effects from the mitochondrial vitamin cocktail (which contain many ingredients available over the counter), the fact that Drs. Kelley and Zimmerman prescribed such treatment carries less weight than the decision to prescribe a drug with known side effects in the face of less than certain diagnosis.

I do not find Dr. Kelley's approach to be a reliable method for diagnosing mitochondrial disease, disorders, or dysfunction. He has not submitted his ideas to a knowledgeable community of peers for judgement; his method has not been widely adopted or recognized as a valid diagnostic approach; and he provided only anecdotal evidence of reproducibility. I reject Dr. Kelley's "bald assurance[s] of validity" and promises that his findings are based on sound science.[234]

Although his approach might prove correct at some future date, it is not "scientific knowledge" just because he says so.[235] He must do the hard work of subjecting it to peer-review and publication and thereby earn the recognition and wide-acceptance he so clearly believes his method deserves. As it stands, his methods and theories cannot be replicated or confirmed.

D. Autism Diagnosis.

I find that A.A. has ASD. That diagnosis is consistent with her entire clinical course, from the pre-vaccination behaviors involving delayed language development, stereotypies, and some lack of social involvement, to the tantrums and disinterest in opening Christmas toys she demonstrated in the December videos, to the diminished interest in play and talking her mother reported in March 2001 at her well-child visit. By the time she saw a speech therapist in August 2001, she displayed enough behavioral differences that the therapist thought she had ASD. The diagnosis was essentially confirmed by Dr. Lavenstein in September 2001. The diagnosis persisted. At the time of the hearing, A.A. was highly functioning, but still displayed issues with social interaction and boundaries.

VIII. Analysis Under *Althen, Pafford* and *Loving*.

The factual underpinnings for petitioners' claims are absent, based on the findings above. I have found that A.A. did not have a mitochondrial disease, dysfunction, or disorder; that she displayed subtle early symptoms of ASD prior to the administration of her October 23, 2000 MMR vaccine; that she did not experience either

[232] Res. Ex. A at 7.

[233] Res. Ex. A at 8.

[234] *See Daubert,* 43 F.3d at 1316.

[235] *See Daubert,* 43 F. 3d at 1315.

an acute illness caused by the MMR vaccination or a sudden regression. The existence of any true regression is unlikely, as Dr. Wiznitzer indicated the term is defined.

A. *Althen* Prong 1: A Reliable Theory.

Althen requires that a petitioner in an off-Table causation case present a reliable medical theory by explaining how the vaccines administered can cause the injury in question. *Althen*, 418 F.3d at 1278. This first prong of *Althen's* three part causation test has also been characterized as the equivalent of the "Can it cause?" inquiry used in toxic tort litigation. *See Pafford*, 2004 WL 1717359, at *4.

The medical theory must be a reputable one, although it need only be "legally probable, not medically or scientifically certain." *Knudsen,* 35 F.3d at 548-49. The Supreme Court's opinion in *Daubert* likewise requires that courts determine expert opinions to be reliable before they may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." 509 U.S. at 590 (footnote omitted). The Federal Circuit has stated that a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly,* 592 F.3d at 1324.

1. Petitioners' Theory

Petitioners claim that A.A.—"born with a susceptibility to mitochondrial metabolism dysfunction, regressed and suffered mitochondrial autism" as the result of her MMR vaccine received on October 23, 2000. *See* Petitioners' Post-Hearing Brief, filed Nov. 27, 2013, at 1. Alternatively, "petitioners allege, the MMR vaccine significantly aggravated [a]n underlying condition, mitochondrial metabolism dysfunction, resulting in mitochondrial autism." *Id.*

The theory that a child with an underlying mitochondrial disorder can experience a febrile illness and thereafter decompensate is not seriously disputed in this claim. However, petitioners' experts significantly expand upon that theory to postulate what amounts to an untested hypothesis. Petitioner's theory has two distinct components: (1) that children with certain specific biochemical findings have a mitochondrial disorder; and (2) that these children can experience a vaccine-caused or aggravated regression and subsequently develop a condition that looks like autism—the "mitochondrial autism" diagnosed by Dr. Kelley. Petitioners have failed to offer preponderant evidence of either component.

a. Specific biochemical findings are not reliable evidence of a mitochondrial disease, disorder, or dysfunction in children.

Doctor Kelley found that A.A. had a mitochondrial disorder based upon certain biochemical findings. However, I have found that the preponderant evidence does not establish that A.A. had a mitochondrial disease, disorder, or dysfunction. The Supreme Court in *Daubert* indicated that scientific knowledge "connotes more than subjective

belief or unsupported speculation." *Daubert*, 509 U.S. at 590. "[T]estimony must be supported by appropriate validation – i.e., 'good grounds,' based on what is known." *Id.* The Supreme Court has provided a non-exhaustive list of factors federal courts may consider, including whether the theory or technique is generally accepted in the scientific community; whether it has been subjected to peer review and publication; whether it can be and has been tested; and whether the known potential rate of error is acceptable. *Daubert*, 43 F.3d at 1316, *on remand from*, 509 U.S. 579 (1993) (citing *Daubert*, 509 U.S. at 592-94).

This diagnosis was based upon biochemical findings that were not interpreted using established criteria, but an unpublished method that has not been peer-reviewed, adopted by other laboratories, or recognized as a valid diagnostic approach by the mitochondrial community at large. It is possible that at some time in the future Dr. Kelley will be able to support his theory that certain biochemical findings are evidence of a mitochondrial disorder, but at this time I find insufficient indicia of reliability for this theory for me to credit it. As Dr. Cederbaum has observed, Dr. Kelley has propounded the theory that these biochemical findings always equate to an electron transport chain dysfunction for 15 years, but has yet to publish the proof. That proof should come before a court relies upon it.

For me, one of the most concerning aspects of the lack of publication and explication to the other experts in the field is that the error rate is unknown. Doctor Kelley's testimony did not convince me that he had established adequate controls. For example, it would be useful to know not only how neurotypical individuals fare on this testing, but how children with other neurological problems, and children with ASD not involving regression fare. I note that in the Theory 2 OAP cases, petitioners relied on a 2004 study by Dr. Jill James showing altered plasma metabolites in children with ASD as compared to age-matched control children. Because 19 of the 20 children with ASD had regression, the authors (and the petitioners) concluded that the altered metabolites contributed to their regression. However, there was no basis to imply that the children with regression were metabolically different from those without regression, as only one child without regression was tested. More fundamentally, the authors noted that children with Down syndrome (an entirely genetic condition) had metabolic profiles more similar to the ASD children to than the neurotypical controls. *See Dwyer*, 2010 WL 892250, at *134 (subpart c, discussing the James studies). I am not considering this study as substantive evidence in this case; I reference it to demonstrate concerns about relying on unpublished data as evidence.

b. No preponderant evidence that the MMR vaccination can cause regression and "mitochondrial autism" in children with mitochondrial dysfunction.

Assuming that I accepted Dr. Kelley's theory that specific biochemical findings are evidence of mitochondrial a disease, disorder, or dysfunction in children—which I do not—petitioners have still failed to present preponderant evidence that that the MMR vaccination can cause regression and "mitochondrial autism" in children with a mitochondrial disease, disorder, or dysfunction. The evidence on this component of

petitioners' theory is too scant to be reliable. Doctor Kelley asserted that in children with mitochondrial dysfunction, inflammation caused by a stressor—such as an infection, a virus, or a vaccine—can cause neurological damage. Tr. at 216-17. Doctor Kelley stated that in his clinical experience, "if there is an identifiable event or identifiable time frame in which regression occurs, the factor that links it is inflammation." Tr. at 217. He opined that cytokines are involved in the inflammatory response—particularly, TNF-α, a cytokine that induces apoptosis, or cell death. Tr. at 216-22. Doctor Kelley asserted "that the peak level of TNF-alpha following immunization with the measles component of the MMR is between 10 and 15 days." Pet. Ex. 23 at 3 (citing Poland, Pet. Ex. 71).

However, Dr. Wiznitzer cogently explained that in Poland, Pet. Ex. 71, for the first 15 days following vaccination—the critical time period according to Dr. Kelley—none of the values for IL-4, IL-6, or TNF-α secretion rose above their baseline. Tr. at 508. Doctor Wiznitzer elaborated "the [Poland] paper itself state[d] that there was no appreciable change in the cytokine levels" for the toddler group. Tr. at 510. There is simply no credible evidence that inflammation caused by vaccination plays a role in the development of regression and/or mitochondrial autism in children with mitochondrial dysfunction. Doctor Zimmerman in fact conceded that "I don't think we can say at this point that in any one individual that inflammation is the cause of autism." Tr. at 320-21.

While it is uncontested that illnesses and other stressors can cause decompensation or regression in children with inborn errors of metabolism, that phenomenon has been observed most frequently in children with urea cycle disorders — a condition that A.A. most assuredly does not have. Whether vaccination can do so, even in these most vulnerable children, has not been established, and the available evidence, most particularly the Morgan study, Res. Ex. C, failed to find evidence that they could.

The most glaring problem, however, is that no evidence adduced in this case, other than the anecdotally based opinions of Dr. Zimmerman, demonstrates that the decompensation or regression induced by illness in children with metabolic or mitochondrial disorders looks like, mimics, or actually results in ASD. Children with ASD may have co-morbid diagnoses of intellectual disability, mitochondrial disorders, seizure disorders, obsessive-compulsive disorders, attention deficit disorders, and many others, but the presence of these other conditions does not automatically equate to a causal relationship.

c. Conclusion

I find that petitioners have failed to present preponderant evidence of a reliable medical theory by explaining how the MMR vaccine can cause or significantly aggravate the injury in question. *Althen*, 418 F.3d at 1278; *W.C. v. HHS*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (discussing significant aggravation.)

B. *Althen* Prong 2: A Logical Connection.

Even if petitioners had provided a theory which satisfied the first prong, to satisfy the second prong of the *Althen* test, petitioners must establish a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. In other words, petitioners must show that the received vaccine did, more likely than not, cause the injury in the case at bar. *Pafford*, 451 F.3d at 1356. The sequence of cause and effect need only be "'logical' and legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548-49; *accord Capizzano*, 440 F.3d at 1326. Evidence from a treating physician may assist petitioner in meeting her burden of proof under the second *Althen* prong. *Capizzano*, 440 F.3d at 1326.

Petitioners have failed to show a logical connection between A.A.'s vaccination and her injury, or the significant aggravation of her injury. Based on the totality of the evidence, as discussed above, I have found that A.A. was not developing normally prior to her vaccination as evidenced by her delayed speech, and abnormal behavior, including hand flapping and limited eye contact on display in the October 14, 2000 video. *See* Section VII. 2, *supra.* After A.A's vaccination, it is unlikely that she experienced the acute febrile illness that petitioners claim. There is no reliable evidence of the type of rapid regression that might signal to a neurologist that something significant had happened. As Dr. Wiznitzer, a specialist who has diagnosed hundreds of children with ASD testified, a precipitous regression would cause him to look for something other than ASD as a cause. However, the evidence in this case supports the slower onset of social and language concerns. In particular, I rely on A.A.'s mother's report at her March 2001 well-child visit, wherein she described problems developing over a period of months, to demonstrate that there was no precipitous or rapid regression. *See* Section VII. 3 and 4, *supra.* Rather, as discussed, I accept the testimony of Dr. Wiznitzer that the behavior exhibited by A.A. on the portions of the October 14 and October 29 videos taken in similar circumstances is strikingly similar; that A.A. exhibited signs and symptoms of autism prior to her vaccination; and that, after her vaccination, A.A. followed the typical course seen in ASD. *See* Section VII. 4, *supra.*

Accordingly, I find that petitioners have failed to establish a logical sequence of cause and effect showing that the vaccination was the reason for the injury" or the significant aggravation of a preexisting injury. *Althen*, 418 F.3d at 1278; *W.C.*, 704 F.3d at 1357.

C. *Althen* Prong 3: A Proximate Temporal Connection.

Merely showing a proximate temporal connection between a vaccination and an injury is insufficient, standing alone, to establish causation. *Grant v. Sec'y, HHS,* 956 F.2d 1144, 1148 (Fed. Cir. 1992). A proximate temporal relationship, even when coupled with the absence of any other identified cause for the injury, is not enough to demonstrate probable cause under the Vaccine Act's preponderance standard. *Moberly*, 592 F.3d at 1323 (citing *Althen*, 418 F.3d at 1278).

Petitioners have failed to establish a proximate temporal relationship between A.A.'s October 23, 2000 MMR vaccination and the onset of her injury, or the significant aggravation of any preexisting injury. Doctor Kelley opined that the "most important fact linking [A.A.'s] deterioration to her MMR vaccination is that the peak level of TNF-alpha following immunization with the measles component of the MMR is between 10 and 15 days." Pet. Ex. 23 at 3 (citing Poland, Pet. Ex. 71). Doctor Kelley testified that "the few children that I've seen who have regressed with – based on evidence that they've regressed with the MMR, it was at 10 to 14 days after the immunization, which . . . [coincides with] the peak cytokine response." Tr. at 225; *see also* Tr. at 279-81 (redirect).

However, as discussed in my *Althen* prong one analysis, Dr. Wiznitzer cogently explained that in Poland, Pet. Ex. 71, for the first 15 days following vaccination—the critical time period according to Dr. Kelley—none of the values for IL-4, IL-6, or TNF-alpha secretion rose above their baseline." Tr. at 508. Doctor Wiznitzer elaborated that "the [Poland] paper itself state[d] that there was no appreciable change in the cytokine levels" for the toddler group, and thus Dr. Kelley's reliance on this article is erroneous. Tr. at 510.

Further, even if petitioners' had established that a medically appropriate time period for the onset of A.A.'s injury was between 10 and 15 days subsequent to her vaccination, I have found no evidence that A.A. experienced an acute illness on October 29, 2000, marked by a spiking fever, continuing for four days, and precipitating a developmental regression. *See* Section VII. 3 and 4, *supra.*

Accordingly, I find that petitioners have failed to demonstrate a medically acceptable proximate temporal relationship between A.A.'s vaccination and injury or the significant aggravation of any preexisting injury.

D. The Additional *Loving* Factors

As disused above, I found that petitioners have failed to establish that A.A. suffered a mitochondrial disease, disorder, or dysfunction. Therefore, petitioners cannot have established that A.A.'s October 23, 2000 MMR vaccination significantly aggravated a mitochondrial disease, disorder, or dysfunction.

However, I will briefly address the additional *Loving* factors necessary to proving such a claim.[236] To demonstrate aggravation of a pre-existing condition, petitioners must show: (1) the vacinee's condition prior to the administration of the vaccine, (2) the vacinee's current condition, and (3) whether the vacinee's current condition constitutes a "significant aggravation" of the condition prior to the vaccination. *See Loving v. HHS*,

[236] The *Loving* test is a six part test. However, the final three parts are virtually identical to the *Althen* factors and are addressed above within my *Althen* analysis.

86 Fed. Cl. 135, 144 (Fed. Cl. 2009) (combining the first three *Whitecotton*[237] factors for claims regarding aggravation of a Table injury with the three *Althen* factors for off table injury claims to create a six-part test for off Table aggravation claims); *see also W.C.*, 704 F.3d at 1357 (applying the six-part *Loving* test.).

In this case I have determined that A.A. was not developing normally prior to her vaccination, as she exhibited signs and symptoms of autism; that A.A. experienced no dramatic regression or acute event following her October 23, 2000 MMR vaccination, and that after her vaccination A.A.'s development followed a course typical of autism. *See* Section VII., *supra.* Accordingly, I find that petitioners have not established that A.A.'s current condition or her condition after vaccination constitutes a "significant aggravation" of her condition prior to her vaccination. Petitioners have satisfied neither the *Althen* test for vaccine causation, nor the *Loving* test for significant aggravation of a pre-existing injury.

IX. Conclusion.

For the reasons discussed above, I find that petitioners have not met their burden under *Althen*. They did not demonstrate any of the *Althen* factors by preponderant evidence. As the United States Claims Court has noted, an expert's "conclusions . . . are only as good as the reasons and evidence that support them." *Davis v. Sec'y, HHS,* 20 Cl. Ct. 168, 173 (1990)*; see also Perreira v Sec'y, HHS,* 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) ("An expert opinion is no better than the soundness of the reasons supporting it.") (citations omitted); *Dobrydnev v. Sec'y, HHS*, 566 Fed.Appx. 976, 982-83 (Fed. Cir. 2014) (an expert's opinion is only worth as much as the facts upon which it is based) (citing *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 242 (1993)); *Fehrs v. United States*, 620 F.2d 255, 265 (Ct. Cl. 1980) (an expert's opinions "can be no better than the soundness of the reasons that stand in support of them").

Petitioners have failed to produce preponderant evidence that the MMR vaccination A.A. received on October 23, 2000, can or did cause her to develop ASD, mitochondrial ASD, or that it can or did aggravate an underlying mitochondrial problem, resulting in ASD or mitochondrial ASD.

Accordingly, the petition for compensation is **DENIED**. The clerk is directed to enter judgment accordingly.

IT IS SO ORDERED.

s/Denise K. Vowell
Denise K. Vowell
Special Master

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[237] *Whitecotton v. Sec'y, HHS*, 81 F.3d 1099, 1108 (Fed. Cir. 1996).